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ASSOCIATE TRAINING PROGRAMS IN THE Medical and Biological Sciences

at the
National Institutes of Health

1976 CATALOG

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NIH
Associate Matching Program
1976 Schedule

April 16	Deadline for receipt of completed applications
June 14 to June 25	Interview period at NIH campus, Bethesda, Md., (by invitation only)
July 12 to July 23	Notification to applicants.

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FOREWORD

The National Institutes of Health conducts and supports research to find better ways of preventing or curing disease and lengthening life. To the Nation's medical and dental schools, universities, and other research centers, NIH provides broad support for biomedical research, research training, and construction of research facilities. This is the NIH extramural program.

NIH conducts laboratory and clinical research in its own facilities primarily on a 306-acre campus in Bethesda, Md. In the past year, over 4,500 patients were admitted for study in the Clinical Center—a research hospital with more than 500 patient beds and 1,100 laboratories. At any one time, more than 1,400 research projects are in progress here on the Bethesda campus and at field offices directed from here. This is the NIH intramural program.

About 2,250 NIH Staff members hold doctorates, 1,100 have M.D. degrees, 1,000 have Ph.D. degrees, and some have both; 46 have D.D.S. degrees and 55 D.V.M. degrees. They and their 3,800 technical assistants represent most of the disciplines that contribute to new medical knowledge.

In this scientific community there are many opportunities for the professional development of physicians and others who intend careers in biomedical research, or in academic medicine. This catalog describes the programs open to Associates at NIH.

P. V. Cardon, M.D.
Associate Director
The Clinical Center

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PART ONE

General Description of Associateships and Other Opportunities

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Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists who receive appointments as Clinical, Research, and Staff Associates at the National Institutes of Health. These positions encompass most of the medical specialties as well as the basic science disciplines.

Appointments to the Associate Training Program are based on intellectual attainment and demonstrated research interest and ability. An individual's background in research is often decisive in making selections but sometimes clinical expertise in a specialty is the main criterion. Selections are made through a matching process, explained on p. —.

Each Associate participates in a research program under the direction of a preceptor. Preceptors help Associates to enrich their experience in research and in other ways. The research responsibilities and latitude given to Associates depend on their capacities, interests, and initiative.

Teaching sessions designed to complement Associateships are held regularly. In addition, postgraduate instruction is available through evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. (See Part Four). Associates in many program areas are expected to take advantage of academic opportunities on the NIH campus.

A candidate may enter the Associate Program as a member of the Public Health Service Commissioned Corps, or as a nontenured civilian employee.

All applicants are carefully considered. NIH welcomes applications from women and members of all minority groups.

The Clinical Associate

The Clinical Associate participates in both clinical and laboratory research. Institute programs differ in the proportion of time devoted to laboratory and clinical responsibilities.

Clinical activities are under the immediate supervision of senior investigators, and include rounds, conferences, and other instructive exercises. The proximity between the patients and collaborating scientists from many biological disciplines has created an unusual environment for clinical investigation. The environment is also enriched by the presence of medical students from all parts of the country with whom

Clinical Associates have close contact and share responsibility for patient care.

Clinical Associates are not in formal residency training programs, even though they may be performing many of the same functions that residents do in other hospitals. Some Associates appointed to Dermatology, Neurology, Psychiatry, and Nuclear Medicine programs are recommended for a limited amount of residency credit by their respective program chiefs. Associates in positions that provide further training in Internal Medicine have often received credit toward their required 3 years of training upon application to the American Board of Internal Medicine—the so-called "short track." However, the Board intends to phase out the short track option. It is doubtful that clinical training completed later than June 1979 will be considered for credit.

The Dental Clinical Associate

Like his physician Clinical Associate counterpart, the Dental Clinical Associate may participate in laboratory and clinical research, and at the same time enhance his professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the Associateship, full opportunity is provided for: (1) familiarity with all ongoing research programs relevant to dentistry; (2) affiliation with one or more preceptors for participation in a mutually acceptable area of investigation; and (3) extension of scientific background through rounds, conferences, seminars and formalized course work.

The Research Associate

The Research Associate devotes most of his time to laboratory research in a biomedical science. His preceptor is responsible for training him in research methodology and design, and for guiding him in the conduct of specific research undertakings and in the interpretation of results. A goal is to select research problems which will enable the Associate to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

In addition, the Research Associate participates in a series of formal tutorial seminars and informal discussion groups designed in content and emphasis for prospective independent investigators. This program provides training in basic medical sciences normally received by Ph.D. candidates but not generally by candidates for the M.D. degree.

The Pharmacology Research Associate

Sponsored by the National Institute of General Medical Sciences, Pharmacology Research Associates spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those who have made a commitment to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

The Staff Associate

The Staff Associate position provides opportunities for those highly qualified candidates who could contribute significantly to research in areas which are not specifically designated in the Research or Clinical Associate categories. The Staff Associate may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he works. Research experience may be supplemented by formal evening study courses, as well as by attendance at lectures by guest speakers and a variety of regularly scheduled seminars.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to students from any of the nation's medical schools. For 1976–77, the staffs of several Institutes are collaborating to supply an in-depth exposure to seven clinical subspecialties: Clinical Psychopharmacology, Endocrinology and Metabolism, Gastroenterology, Immunology, Infectious Diseases, Oncology-Hematology, and Surgical Oncology.

The essence of this educational experience is a close association between the student, clinical associates, and physician-scientists in several of the Institutes.

Students have patients assigned to them for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Electives for individual students with particular interests in fields other than those listed above are sometimes arranged through communications between an NIH staff member and a faculty sponsor of the student.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

P. V. Cardon, M.D.
Associate Director, Clinical Center, and
Chairman, Committee on Specialty Electives
National Institutes of Health
Bethesda, Md. 20014

Residency Programs

Fully approved residency programs are offered in clinical pathology, anatomical pathology, and combined clinical and anatomical pathology. In 1974 the American Medical Association established requirements for a residency in blood banking; it is anticipated that a blood bank residency program will be functioning as of 1976.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Ronald J. Elin, M.D., Ph.D.
Chief, Clinical Pathology Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

Louis B. Thomas, M.D.
Chief, Laboratory of Pathology
National Cancer Institute
National Institutes of Health
Bethesda, Md. 20014

Paul V. Holland, M.D.
Chief, Blood Bank Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

On the basis of agreements between program chiefs and appropriate American Specialty Boards, Clinical Associates in dermatology, psychiatry, and neurology may receive credit for 1 year each, and 2 years in nuclear medicine. Associates in internal medicine also may receive credit toward their required 3 years of training upon application to the American Board of Internal Medicine.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as Associates, but as Staff Physicians. Initial appointments are temporary and usually for 2 years, but some Staff Physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part time in ongoing research.

PART TWO

Applying for an Associateship

About 100 Clinical Associates and 50 Research and Staff Associates are appointed annually. Associates may be employed through the Commissioned Corps of the Public Health Service or through a Civil Service mechanism. Of course, if applying through Civil Service, it is not necessary to submit the PHS commissioning forms.

Applicants usually apply during their third or fourth year of medical school for entrance on duty two years later. However, some Associate positions are appropriate for persons currently in their intern or residency training. The applicant should designate on his application the year or years he wishes his associateship to begin. Most appointments will be for 1978, and a few will be available for 1977.

To be considered for a Clinical, Research, or Staff Associate appointment, the following forms must be received in the NIH Associate Office, National Institutes of Health, Bethesda, Md. 20014:

- Information Record for Clinical, Research, and Staff Associate Positions;
- Program Area Selection Check List;
- NIH Associate Information and Status Record;
- Interview Information Record;
- Application for Appointment as a Commissioned Officer in the Public Health Service (2 copies);
- Fingerprint Chart (fingerprints may be obtained at PHS facilities, local police, or post office);
- Data for Nonsensitive or Noncritical Position.

The applicant is responsible for requesting the following materials to complete the application.

- Three sets of references from professional persons whom the candidate has listed on the NIH information sheet. Each set consists of: (1) Request for Confidential Evaluation of Applicant for Appointment as an NIH Associate; and (2) Reference Request (Commissioned Corps).
- Two copies of all college and medical or dental school transcripts (showing class standing, if available).

Public Health Service Commissioned Corps

The Commissioned Corps is a uniformed service similar in many respects to the Army, Navy, and Air Force. It is a uniquely "all officer" Corps, comprised largely of professionals in medical and health related fields.

Pay, allowances, and other benefits are comparable to those of officers of the Armed Forces. Benefits include medical care for officers and dependents; tax-free allowances for quarters and subsistence; commissary, post exchange, and officers' club privileges; and 30 days annual leave.

While most career PHS officers are eligible for the variable incentive pay (VIP) "bonus," VIP is not an immediate incentive to prospective Associates. Officers serving in their first 2 years as Associates, and officers performing obligated service incurred through participation in Senior COSTEP Program are *not* eligible for VIP.

For those considering longer periods of service or careers in the PHS, the advantages of subsequent VIP, and of noncontributory retirement and survivor benefit plans are substantial.

To be eligible for the Commissioned Corps for participation as an NIH Associate, a candidate must meet the following requirements:

1. Be a United States citizen.
2. Meet the medical fitness standards.
3. Be a graduate of an accredited medical or dental school.
4. Satisfactorily complete an internship approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)

Civilian Staff Fellowships

As an alternative to the Commissioned Corps, Associates may be appointed as Staff Fellows. This is a temporary Civil Service appointment. Salaries are similar to those of Commissioned Corps officers who do not receive the variable incentive pay "bonus." Medical fitness standards are less stringent, and noncitizens of the United States who are eligible for naturalization within 4 years may be appointed. Usually, Fellows earn slightly less annual leave. Comparative advantages of retirement plans and fringe benefits depend largely on individual circumstances and preferences.

Early Commissioning Program for Medical Students (PHS Senior COSTEP Program)

Qualified candidates who will be in their senior or last year of medical school during academic year 1976–77 may apply for an Associateship through this program. Candidates may apply for duty to begin either

(1) following one or more years of residency training or (2) immediately after internship.

Successful candidates are appointed and placed on active duty as commissioned officers in the Reserve Corps of the Public Health Service during their senior or final year. They receive full pay and allowances as Junior Assistant Health Service Officers (equivalent to Navy Ensign), plus payment of tuition, fees, and other related expenses. In return for this financial support, they are obligated to serve on active duty as medical officers with the PHS for a minimum of 2 years.

Applications cannot be considered from members of another uniformed service or anyone having a service commitment upon graduation other than to the Public Health Service.

Method of Selection—Matching Program

Selections for the Clinical, Research, and Staff Associate appointments are made through a matching process in which the candidate's preferences are matched with the Institute preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Check List." After reading Part Three of this catalog, he should check off on these sheets the areas in which he is interested. He does not indicate his preferences at this point, and he is not limited to any particular number of choices. The check marks that he makes will determine the laboratories and branches to which his application will be circulated at the National Institutes of Health.

After thorough review of all applications by the Institutes, a limited number of candidates will be selected for personal interviews. NIH will pay air fare of those selected for interviews who elect to apply for Staff Fellow (civilian) appointment.

The NIH Associate office will set up the interviews and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

PART THREE

Program Areas for Which Candidates May Apply

EACH of the major NIH components has prepared a description of its program areas for which Associates may seek appointment. Due to diversity of the operations and programs within these major components, the descriptions do not follow a pattern. In effect, however, all of these descriptions are meant to anticipate the questions which applicants may have in selecting the program areas for which they wish to be considered. It should be noted that a candidate is not limited as to the number or kinds of positions for which he may apply.

National Cancer Institute

Director, Frank J. Rauscher, Jr., Ph.D.
Clinical Director, Vincent T. DeVita, Jr., M.D.

Laboratories and Branches

Director, Division of Cancer Biology and Diagnosis, Alan S. Rabson, M.D.
  Associate Director for Program Planning, Irvin C. Plough, M.D.
    Chief, Laboratory of Biochemistry, Robert F. Goldberger, M.D.
    Chief, Laboratory of Biology, Walter E. Heston, Ph.D.
    Chief, Laboratory of Cell Biology, Lloyd W. Law, Ph.D.
    Chief, Laboratory of Immunodiagnosis, Ronald B. Herberman, M.D.
    Chief, Laboratory of Molecular Biology, Ira H. Pastan, M.D.
    Chief, Laboratory of Pathology, Louis B. Thomas, M.D.
    Chief, Laboratory of Pathophysiology, Pietro M. Gullino, M.D.
    Acting Chief, Laboratory of Theoretical Biology, Mones Berman, Ph.D.
    Chief, Dermatology Branch, Marvin A. Lutzner, M.D.
    Chief, Immunology Branch, William D. Terry, M.D.
    Chief, Metabolism Branch, Thomas A. Waldmann, M.D.
Director, Division of Cancer Treatment, Vincent T. DeVita, Jr., M.D.
  Deputy Director, Stephen K. Carter, M.D.
  Clinical Director, Vincent T. DeVita, Jr., M.D.
  Deputy Clinical Director, John L. Ziegler, M.D.

Clinical Oncology Program, Vincent T. DeVita, Jr., M.D.
  Chief, Medicine Branch, Robert C. Young, M.D.
  Chief, Pediatric Oncology Branch, Arthur S. Levine, M.D.
  Chief, NCI-VA Medical Oncology Branch, John D. Minna, M.D.
  Chief, Radiation Oncology Branch, Ralph E. Johnson, M.D.
  Chief, Surgery Branch, Steven A. Rosenberg, M.D.

Cancer Therapy Evaluation Program, Franco Muggia, M.D.
  Chief, Investigational Drug Branch, Milan Slavik, M.D.
  Chief, Combined Modality Branch, Franco Muggia, M.D.

Experimental Therapeutics Program, Vincent T. Oliverio, Ph.D.
  Chief, Laboratory of Chemical Pharmacology, Richard A. Adamson, Ph.D.
  Chief, Laboratory of Toxicology, Anthony M. Guarino, Ph.D.
  Chief, Laboratory of Molecular Pharmacology, Kurt W. Kohn, M.D., Ph.D.
  Chief, Laboratory of Tumor Cell Biology, Robert C. Gallo, M.D.

Drug Research and Development Program, Saul A. Schepartz, Ph.D.
  Chief, Drug Development Branch, Harry B. Wood, Jr., Ph.D.
  Chief, Drug Evaluation Branch, John M. Venditti, Ph.D.
  Chief, Laboratory of Experimental Chemotherapy, Abraham Goldin, Ph.D.
  Chief, Laboratory of Medicinal Chemistry & Biology, David D. Johns, Ph.D.

Baltimore Cancer Research Center, Michael D. Walker, M.D.
  Chief, Laboratory of Pharmacology, Carl C. Levy, Ph.D.
  Chief, Clinical Branch, Michael D. Walker, M.D.

Division of Cancer Biology and Diagnosis

A broad range of research is carried out in both basic laboratories and clinical branches under the general direction of Dr. Alan S. Rabson.

The Laboratory of Biochemistry consists of six sections. The Cellular Regulation Section is concerned with the molecular mechanisms by which steroid hormones regulate specific gene expression in eukaryotes. The system under investigation is egg yolk phosphoprotein synthesis in the liver of the rooster after treatment with estrogen. This system has the advantages of a hormonal response that is highly specific and of great magnitude in a tissue capable of a wide diversity of genetic expression. The approach involves studies with purified components *in vitro* as well as with cultured cells and whole animals.

The NUCLEIC ACID ENZYMOLOGY SECTION is concerned with the study of nucleic acid metabolism and structure. Systems under study include the replication of Simian Virus 40 DNA in permissively infected monkey cells; the structure and origin of defective Simian Virus 40 DNA containing host DNA sequences; bacterial polynucleotide phosphorylase; cyclic AMP metabolism; the role of histone 1 in chromatin structure. Emphasis is placed on reaction mechanisms by two main approaches: (1) structure of substrates and products; and (2) relation of protein structure to function. A variety of modern techniques of nucleic acid and protein chemistry are employed.

The BIOCHEMISTRY OF GENE EXPRESSION SECTION studies control of gene expression in eukaryotic cells and its application to clinical medicine. The effects of steroid hormones on enzyme induction both in cultured cells and cell hybrids are investigated, along with studies on steroid receptors in human leukemia and breast cancer. Techniques of cell culture, cell fusion, chromosome banding, protein synthesis, and affinity chromatography are among those utilized.

The BIOSYNTHESIS SECTION conducts research on the synthesis, assembly, and functional properties of cellular membrane systems. Current studies deal with regulation of collagen biosynthesis, the properties of membrane-associated DNA polymerases, alterations in synthesis of membrane "structural" proteins in transformed cells, and electron microscopy of surfaces of cells interacting in the immune response.

The CELL PHYSIOLOGY AND ONCOGENESIS SECTION investigates cellular and molecular events in the neoplastic transformation of mammalian cells in culture. The goals of this section include early detection of neoplastic transformation and elucidation of the cause and effect relationships in oncogenesis. Among the tools employed are long-term tissue culture, modern biochemical methods, animal transplantation, microscopy-photography, and radioisotopic techniques.

The PROTEIN CHEMISTRY SECTION is investigating biochemical changes accompanying the maturation of granulocytes in bone marrow, interactions between cells involved in the immune response, and the transfer of genetic information through the cellular uptake of isolated chromosomes. Tissue culture, protein fractionation, cell separation and radioisotopic procedures are employed.

In the LABORATORY OF BIOLOGY, carcinogenesis is studied in the broad biological sense. Attention is given to the manner in which genetic, viral, hormonal, and immunological factors as well as chemical and physical carcinogens lead to the occurrence of cancer. Special emphasis is given to the mammary tumor system in mice—the morphologic and biochemical nature of the virus particle, the identification of various lines of the virus, and its genetic transmission. An additional area of study is the regulation of oncornaviral expression in mammalian cells. In particular, cell hybridization and chromosome segregation are used to induce viral replication in primate cell cultures. This work is supported with other basic studies in cytology and biochemical genetics.

Personnel of the LABORATORY OF CELL BIOLOGY have diverse interests focusing upon the study of transformation of a normal cell to a neoplastic cell. Techniques from the fields of virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization, and electron microscopy are used. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells (principally plasma cells), role of cell membranes in regulating differentiation and growth, identification and study of tumor antigens and of the specific immune reactions initiated, solubilization and purification of transplantation and tumor antigens, influence of somatic cell hybridization on expression of genetically determined events, and ultrastructural analysis and molecular biology of viral oncogenesis.

The LABORATORY OF IMMUNODIAGNOSIS conducts studies on the nature of tumor associated antigens and other cell surface antigens on tumor cells and on the immune response to these antigens. The antigens in several tumor systems, both in animals and in man, are being studied, particularly in regard to their role in host resistance against tumor growth and their possible diagnostic applications. The cell-mediated and humoral immune responses to a variety of experimental and human tumors are being extensively studied. The assays for cellular immunity include radioisotopic and visual cytotoxicity assays, lymphocyte stimulation, migration inhibition, and skin tests for delayed hypersensitivity. The interrelationships among these assays and the usefulness of each for the diagnosis of cancer and for monitoring of tumor-bearing individuals are being investigated.

The program offers the opportunity to perform research in experimental tumor systems and/or to perform immunologic investigations on patients with cancer.

The LABORATORY OF MOLECULAR BIOLOGY investigates gene function and other regulatory mechanisms in animal and bacterial cells. Studies are devoted to identifying factors which regulate cellular behavior and alter gene expression. One molecule of particular interest that controls the behavior of both bacterial and animal cells is cyclic AMP.

Cyclic AMP controls growth rate, shape, adhesiveness, agglutinability, motility, and macromolecular synthesis in cultured fibroblastic cells. Transformed cells have low levels of cyclic AMP, and these low levels account for some of the abnormal properties of such cells. Current studies are directed towards elucidating why transformed cells make less cyclic AMP and understanding how cyclic AMP controls the behavior of these cells.

Efforts are also being directed toward exploration of factors regulating the organization of subcellular organelles in cells, including their position, number and turnover rates, and how they cooperate in cell function. Processes such as cell growth, macropinocytosis, exocytosis, and transport of proteins within cells are of particular interest. Finally, investigations are being carried out on how cells interact in organ growth and function.

The regulation of gene expression is studied using cell-free systems containing purified proteins and specific bacterial and viral genes. Mutants defective in transcription are isolated and employed to detect new regulatory compounds or to elucidate regulatory mechanisms. The nucleotide sequence of genetic regulatory regions is also under study.

Other efforts are directed towards investigating the molecular basis of genetic recombination. These studies employ the bacteriophage λ and its host, *E. coli.* Mutants defective in recombination are isolated and the nature of their defects analyzed by both genetic and biochemical methods.

Some of the actions of cyclic AMP are on the cell membrane and may involve alterations in the activity of myosin, actin, tubulin, and related proteins.

The LABORATORY OF PATHOLOGY of the National Cancer Institute offers a 2-to-4-year training program for residents in pathologic anatomy in the Clinical Center, National Institutes of Health, Bethesda, Maryland. The program which is fully approved for Board certification provides well supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology and neuropathology can be arranged. Opportunity is provided for learning many research techniques, particularly electron microscopy, fluorescence microscopy, tissue culture, histochemistry, autoradiography, and cytogenetics. Individual or collaborative participation in clinical or laboratory research projects by the residents and selected Research Fellows and Visiting Scientists is encouraged.

In addition to the autopsy, surgical pathology, and cytodiagnostic services, the laboratory also carries on a broad research program in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

LABORATORY OF PATHOPHYSIOLOGY. The SECTION ON CELLULAR AND MOLECULAR PHYSIOLOGY studies the biochemical mechanisms which control the early stages of cell growth induction in normal and neoplastic human cells. Emphasis is on the mechanisms which maintain physiologically resting cells in the non-growing condition and the early biochemical modifications which occur on growth stimulation. Current studies include characterization of translational controls in resting human lymphocytes, examination of facets of messenger RNA metabolism which are unique to physiologically resting cells, and studies of the regulation of the production of specific proteins whose synthesis is related to the onset of lymphocyte growth.

The SECTION ON CELL CYCLE REGULATION is concerned with the characterization of biological events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the synthesis of oligo (ADP-ribose), the activity of the enzyme complex synthesizing the oligomer, and the effect of a change in its concentration on the cell cycle.

The SECTION ON MEMBRANE BIOLOGY carries on work in the field of freeze-fracture of plasma membrane with particular emphasis on intramembranous particles, their aggregation and biological significance. Another group of projects concerns the process of mammary tumor regression, the role of hormonal deprivation of the host on cell survival, and the effect of cAMP on the initiation and progression of tumor regression.

The LABORATORY OF THEORETICAL BIOLOGY is concerned with the formulation of theories of structure, function, and dynamics of biological systems and with the development of mathematical and computational techniques for the analysis of those systems. Of particular interest is the development of formal models for the kinetics of metabolites and hormonal regulation systems. Studies are also conducted on membrane structure and function, transport through artificial lipid bilayer membranes, and on configurations and properties of polypeptides and other macromolecules. Although the group is predominantly theoretical, experimental work related to the problems being investigated is carried out within the laboratory and in collaboration with experimental groups.

The DERMATOLOGY BRANCH conducts both clinical and basic research, studying the causes and treatment of malignant diseases of the skin and the host's response to these diseases. Studies are designed to identify and characterize the biologic behavior of epithelial and lymphoid tissues in normal and pathologic circumstances using the techniques of biochemistry, immunology, virology, scanning and transmission electron microscopy, and tissue culture. The chemistry, structure, and function of keratins, melanins, and cell organelles are being investigated. Studies of the pathological processes in genetic skin diseases, such as xeroderma pigmentosum, continue to elucidate mechanisms which are involved in human carcinogenesis.

In the IMMUNOLOGY BRANCH, clinical and basic science approaches are combined in the study of immune responses to normal and malignant cell surface antigens. Fundamental investigations stress mechanisms of normal and disordered immune responses and modes of specifically modifying those responses. Immunochemical, biochemical, serologic, immunogenetic, and tissue culture techniques are applied to research on the structure and function of antibodies and cell surface receptors, and the genetic control of immune responses. A variety of animal models is used in the study and characterization of histocompatability antigens, differentiation antigens, tumor specific antigens, and cell surface antigens of possible importance in cellular cooperation. Clinical interests include immunotherapy of malignant disease, transplantation immunology, and *in vitro* correlates of immunity in disease states and during therapy.

The METABOLISM BRANCH is studying the metabolic and immunologic antecedents and consequences of cancer. Investigations are directed toward a broad range of immunological problems, especially as they involve immunodeficiency states in man associated with a high incidence of malignancies. The studies are concerned with the mechanisms of abnormalities of circulating and cellular immune responses in patients with such disorders as agammaglobulinemia, the Wiskott-Aldrich syndrome, ataxia telangiectasia, intestinal lymphangiectasia, and inflammatory bowel disease. Special attention is given to the study of cell cooperation in the immune response, factors controlling differentiation of cells, on membrane associated receptors of lymphoid cells, on mechanisms of lymphocyte mediated cytotoxicity, on the role of macrophages and of suppressor T cells in controlling the immune response and on factors controlling immunoglobulin metabolism.

Another major area of interest of the Metabolism Branch is the study of endocrine and metabolic derangements in a variety of human diseases. These studies are concerned with the molecular etiologies of hepatic and erythropoietic porphyria, growth retardation due to growth hormone deficiency, abnormalities of bone and collagen metabolism, disorders of amino acid metabolism and abnormalities of serum protein metabolism. The emphasis is on the regulation and biochemistry of the enzymes of porphyrin, proline, and collagen metabolism and the biochemical mechanisms of action of growth hormone and related growth factors studied *in vitro*. Human and animal cells in tissue culture are used for biochemical studies defining genetic defects and elucidating humoral and cellular agents which alter gene expression and enzyme activity.

Division of Cancer Treatment

An intensive program of laboratory research and clinical investigation concerned with the therapy of cancer is under the direction of Dr. Vincent T. DeVita, Jr.Emphasis is placed on combinations of drugs with other modalities of therapy including surgery, radiation, and immunotherapy.

Cancer Therapy Evaluation Program is involved in the planning and directing of the Clinical Contract Program, testing combined modality therapy approaches, and the clinical evaluation of new investigational cancer chemotherapy agents. Direction is also given to the evaluation of the effectiveness of specific types and methods of cancer therapy.

The Combined Modality Branch implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide specific and immediate clinical trials of combined modality approaches to the therapy of specific tumors. It is responsible for bringing together, under contract, expertise in chemotherapy, surgery, radiotherapy, and immunotherapy in the design of comprehensive therapeutic programs geared to the eventual cure of specific disease entities. It is responsible for maintaining continuing liaison with various advisory and consultant groups established as working committees to study the effectiveness of specific types and methods of cancer therapy.

The Investigational Drug Branch implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide highly specific and immediate clinical trials of anticancer drugs that have demonstrated high activity in animals in the preclinical phase of the drug development aspect of the Cancer Therapy Program. The Branch is responsible for the communication and filing of all information required by the Food and Drug Administration in connection with the Drug Development Program of the National Cancer Institute.

The CLINICAL ONCOLOGY PROGRAM consists of the Medicine Branch, the Pediatric Oncology Branch, the Radiation Oncology Branch, the Surgery Branch, and the NCI-VA Medical Oncology Branch.

The MEDICINE BRANCH is a medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, breast cancer, ovarian carcinoma, sarcomas, melanoma, cancer of the pancreas, chronic leukemias, and myeloproliferative disorders. Training in clinical diagnostic procedures related to cancer, such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH including cancer surgery and radiation therapy. The Branch conducts weekly clinical conferences with the departments of Radiation Oncology, Pathology, Clinical Pathology (Hematology), and Radiology on current problems and on the staging of lymphomas. The research program focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. Collaboration with the Laboratory of Pharmacology and other groups concerned with marrow culture is maintained.

In addition, an active research program is maintained in the field of hormone receptors, tumor markers, and tissue culture.

The PEDIATRIC ONCOLOGY BRANCH practices a combined modality approach to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, neuroblastoma, aplastic anemia, and histiocytosis. Three areas of clinical investigation are stressed: (a) chemotherapy and immunotherapy; (b) hematologic support and bone marrow transplantation; and (c) diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The Branch is particularly interested in the psychosocial aspects of cancer, and training in this area is emphasized. Candidates with prior training in medicine or in pediatrics may apply to this Branch and may be Board eligible in medical oncology or in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical means followed by chemoimmunotherapeutic manipulations, the goal of which is significant prolongation of remission. Comprehensive immunological essays are performed in order to assess the utility of various techniques in understanding the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. A major area of interest is hematologic reconstitution through allogeneic, isogeneic, and autologous bone marrow transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised host. These maneuvers include the use of laminar-air-flow isolation and prophylactic antimicrobial agents. Studies on microdetermination of circulating endotoxin and on the molecular identification of latent viral genetic material illustrate newer diagnostic approaches to infectious disease.

In the second and optional third year of this program, clinical research training is offered in the three areas previously described. In addition to clinical research, this Branch has a strong program in basic laboratory investigation with emphasis on the molecular biology of tumor viruses, tumor cell biology, molecular and clinical pharmacology, tumor immunology, and immunohematology. Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates, utilizing excellent collaborative relations with other Branches of the NIH.

The RADIATION ONCOLOGY BRANCH is a multidisciplinary unit comprised of a medical oncology and radiation oncology staff. Combined modality approaches are emphasized using chemotherapy, radiation therapy, and immunotherapy. The clinical training in the management of malignant disease involves not only use of the nonsurgical methods of treatment but affords experience with various diagnostic procedures including bone marrow biopsy, liver biopsy, peritoneoscopy, and fiberopticbronchoscopy. The two-year program involves nine months of ward (inpatient) assignment and elective rotations through tumor pathology, radiation therapy, hematology, and to Medicine, Pediatric, Surgery or VA Medical Oncology Branches. Fellows have clinic (outpatient) responsibilities during the entire two-year period to provide opportunity for longitudinal observation and management of cancer patients. While clinical research programs concentrate on hematologic diseases (chronic leukemia, malignant lymphomas, and Hodgkin's disease), lung cancer, malignant bone tumors, and soft tissue sarcomas, experience is gained with a wide spectrum of cancer by virtue of collaborative studies and assignment of each fellow to the consultation service for several months.

The SURGERY BRANCH is a surgical oncology unit emphasizing a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen including melanomas, sarcomas, rectal cancers, pancreatic cancers, and head and neck cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy as well as the development of new surgical techniques. The laboratory efforts of the Surgery Branch are closely related to its clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The Branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, x-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch staff also serve as general surgeons to the entire National Institutes of Health and see a variety of general surgical consultations not related to the field of cancer.

The NCI-VA Medical Oncology Branch is located outside the Clinical Center at the Veterans Administration Hospital in northwest Washington, D.C. This Branch is concerned with the primary care and clinical investigation of patients with a wide variety of solid tumors and hematologic malignancies. A major effort involves the staging and treatment of small cell carcinoma of the lung. In addition to lung cancer, treatment protocols of head and neck, stomach, pancreatic, colorectal, and prostatic carcinoma are underway. Fellows become experienced in diagnostic procedures, such as bone marrow biopsy, liver biopsy, fiberoptic bronchoscopy, and peritoneoscopy. Programs in the treatment of both acute and chronic leukemias, myelomas, lymphomas, and pre-malignant hematologic syndromes are being developed with the division of hematology. Both veteran and nonveteran patients are admitted for study, and the Branch provides oncology consultation for the hospital.

The Branch laboratory investigations in human tumor cell biology involve studies of oncogenic viruses, molecular biology, cell culture, somatic cell hybridization, and human tumor cell genetics and cytogenetics. *In vitro* models for chemotherapy are under study and clinical investigation of tumor cell kinetics is carried out. The fellowship program is designed to include both clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual fellow's interest and goals. To further this end, close ties and collaboration with the NH community in Bethesda are maintained.

The Experimental Therapeutics Program studies many facets of the interaction between drugs and living materials. It includes biochemical pharmacology, toxicology, physiological disposition, drug metabolism, molecular biology, mechanism of action, and comparative pharmacology. In addition, it works closely with the Medical Oncology Program with regard to clinical research problems.

The Office of the Associate Director, in addition to an overall administrative responsibility for four laboratories, conducts a research effort in the area of the exchange of various physiological and pharmacological substances between blood, cerebrospinal fluid, and brain extracellular and intracellular fluids. Both experimental and computer studies are designed and executed in attempt to increase our understanding of the basic transport mechanisms involved in the system and to examine the delivery of drugs to normal tissue and tumor sites within the brain, spinal cord, and meninges. These efforts are intended to elucidate new and better routes of drug administration, find key physicochemical and structural properties of potential chemotherapeutic agents which will optimize tissue delivery, and develop ways to transiently modify the "transport barriers" and subsequently increase drug uptake. Another important area of research concerns biochemical pharmacology of antitumor drugs in preclinical systems, an effort which blends well with ongoing activities in the laboratories within the EXPERIMENTAL THERAPEUTICS PROGRAM.

The LABORATORY OF TOXICOLOGY functions to investigate and describe the qualitative and quantitative toxicity of potential antineoplastic drugs using animal test systems. Young and old animals of both sexes, as well as pregnant animals are included in these studies. Treatments range from acute to chronic. Adverse effects of oncolytic agents in man are correlated with those observed in lower species in an effort to increase the predictability of the animal test systems. Attempts are made to define the predictability, reversibility, and mechanisms of drug-induced toxicity. The pathogenesis of the lesions detected is studied at every level from the morphologic to the molecular. Wherever possible, antidotes are sought. In order to achieve the greatest therapeutic effect at the least cost in serious side effects, a variety of experimental treatment regimens are tested. The LABORATORY OF TOXICOLOGY also investigates whether proposed drug combinations alter toxicity and therapeutic efficacy by evoking changes in drug binding, absorption, distribution, and/or metabolism. The laboratory is composed of three scientific units: Biochemistry, Comparative Pathology and Drug Interactions. All the functions of the laboratory are closely integrated with the development of new anticancer agents and ongoing clinical studies.

The LABORATORY OF MOLECULAR PHARMACOLOGY is engaged in fundamental studies on the mechanisms of drug action on mammalian cells, particularly actions involving nucleic acids and related structures. Of major interest are (1) interactions between drugs and macromolecules studied by physical chemical techniques, (2) effects on the synthesis and function of nucleic acids and related structures in cells, and (3) relations between molecular effects of drugs and their biological effects on cells. The drugs studied are actual or potential chemotherapeutic agents or compounds having special properties that facilitate relevant studies of intracellular processes.

The Laboratory of Chemical Pharmacology is primarily engaged in studies of the pharmacology of new and established antitumor agents and other drugs used in patients with cancer. Clinical Associates assigned to this area spend their first year as primary physicians on the wards of the Medical Oncology Area. During the second year, they participate in laboratory research projects under the direction of a senior investigator in the LABORATORY OF CHEMICAL PHARMACOLOGY. A wide range of research topics related to the pharmacology of antineoplastic agents is under active investigation. Particular emphasis is placed on the pharmacokinetics and cellular transport of the agents, the effect of the agents on the cell cycle, the disposition of antitumor agents in animals and man and the enzyme systems involved in the metabolism of the antitumor agents. Other studies include mechanisms of resistance to anticancer agents; structure activity relationships of antitumor agents; new approaches to cancer chemotherapy; the untoward effects of drugs resulting from inherent physical-chemical properties and/or interactions with other concomitantly used drugs; and biological markers which will aid in the diagnosis and treatment of the precancerous state as well as frank neoplasia. Agents of recent interest have been maytansine, inosine dialdehyde, gallium, alanosine, nitrosoureas, rifampicin analogs, interferon and interferon-inducers, carboxypeptidase G_1, DNA and RNA binding antibiotics, hycanthone, and the folic acid antagonists. Biological markers of recent interest have been alpha-fetoprotein, carcinoembryonic antigen, methylated nucleic acid bases, HCG, polyamines, and sialic acid. In all areas of interest, both fundamental and pragmatic approaches are utilized.

The LABORATORY OF TUMOR CELL BIOLOGY has several major research interests including studies on: (1) the controls of cellular growth, differentiation, maturation, and the process of malignant transformation in mammalian cells; (2) mechanism of action of new antitumor agents and elucidating alterations involved in the development of resistance to drugs; (3) development of molecular probes for the presence of small numbers of neoplastic cells; (4) purification and biochemical and biological characterization of DNA polymerases from human cells and from oncogenic RNA viruses ("reverse transcriptase" or RNA-dependent DNA polymerase). These studies are designed to aid in the understanding of the function of these enzymes, *e.g.*, appearance in the cell cycle, activity with certain compounds, role in cellular differentiation, and role in neoplastic transformation. The questions of whether any of the enzymes in cells are viral in origin and whether DNA and RNA polymerases of neoplastic cells differ qualitatively or quantitatively from those of normal cells are under intense study; (5) development of new molecular probes for virus specified information in cells; (6) new antiviral agents are evaluated in a number of biological and biochemical systems; and (7) attempts to elucidate the origin and evolution of RNA tumor viruses and if information from these viruses is involved in the etiology of human neoplasias. Overall the major goals may be summarized as attempts to develop new approaches for diagnosis, prognosis, and therapy of human neoplasia based on information derived from basic studies on neoplastic cells and on the conversion *in vitro* of normal cells to neoplastic cells.

The DRUG RESEARCH AND DEVELOPMENT PROGRAM is engaged in a multidisciplinary approach to the fundamental and developmental aspects of cancer chemotherapy. Through contracts and direct laboratory operations it carries out programs directed toward the development of new and better antitumor agents.

The LABORATORY RESEARCH PROGRAM within the immediate office involves correlation of fundamental laboratory investigations with preclinical developmental and clinical investigations. Surveillance of research and new drug development is undertaken on an international scale and includes maintenance of chemotherapy offices in Europe and Japan. Selected collaborative research programs are concerned with fundamental chemotherapeutic, biological, biochemical, and immunological investigations of the mechanism of action of antitumor and antiviral agents, new therapeutic models, metastasis, drug resistance, combined modalities, animal genetics and disease control.

The DRUG DEVELOPMENT BRANCH is responsible for the development of more effective chemical agents for human cancer chemotherapy, primarily through contract-supported projects. It supervises the procurement, chemical preparation, and quality control of bulk and formulated drugs tested and evaluated. New agents are prepared by laboratory synthesis or they are derived from natural products. Active compounds may be modified to increase their therapeutic effectiveness and to lessen their toxicity. Theoretical designs, particularly for drugs that may be useful for the slower growing tumors, are explored. Research efforts are also directed towards the analysis of structure-activity patterns and towards dealing with dosage and solubility problems. Computer-assisted programs for chemical data processing and information storage and a worldwide search for potential antitumor agents are major activities of the Branch.

The DRUG EVALUATION BRANCH is engaged in a broad approach to the recognition of potential new anticancer drugs and to fundamental and developmental aspects of antitumor therapy. Studies include: testing of unknown materials for biological activities of predictive value to the clinic; detailed evaluation of drugs as potential clinical candidates with respect to optimal usage, including treatment route and schedule, combination chemotherapy, and combined treatment modalities; mechanisms of drug action and other biochemical and cellular kinetic aspects of cancer chemotherapy; the influence of physiological disposition and metabolism on therapeutic efficacy; the investigation of specific problems that emerge from toxicological studies in large animals or in early clinical trial; mechanisms of drug resistance and means of overcoming resistance; establishment of new therapeutic principles and procedures for the management of tumor growth in animals; structure-activity relationships; the development of new and improved *in vivo* and *in vitro* assays for drug evaluation including disease-oriented tumor models; the development and use of computer systems for processing the data generated.

The LABORATORY OF EXPERIMENTAL CHEMOTHERAPY undertakes fundamental studies of the biology of normal and tumor cells in chemotherapy; investigation of the fundamental basis of drug specificity; study of sensitivity differences and control mechanisms in the cell cycle; basis and therapy of invasiveness and metastasis; rational modification of structural analogs and structure-activity analysis, study of the basis of resistance and cross-resistance to antitumor agents; development of new models for drug evaluation; combination chemotherapy; surgical adjuvant chemotherapy; radiation plus chemotherapy; investigation of host immunological factors in tumor growth; studies of the combined effects of immunity and chemotherapy involving active, passive, adoptive or nonspecific types of immunotherapy; antigenic alteration plus chemotherapy in relation to collateral sensitivity. The studies are correlated with the clinic in the development of modalities of therapy, special problems, and therapeutic principles.

The LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY conducts an integrated program for the development of new antitumor agents. The synthesis of compounds with potential antitumor activity is carried out, and the effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo*, and on a variety of subcellular target sites, e.g., nucleic acids, cell membranes, microtubular protein, enzyme systems. Flexibility in the development of new biological test systems of predictive value to the medicinal chemistry program is emphasized. The Laboratory develops analytical methodology for *in vivo* studies with new agents, and, where warranted, extends biological studies with such agents to the preclinical and initial clinical Phase I stages. In addition, the Laboratory manages a contract-supported program to characterize the mode of action of new antitumor agents at the molecular and cellular level. The Laboratory stresses the rapid and continuous utilization of the data generated from intramural and collaborative biological studies for the elucidation of structure-activity correlations and for guidance in the synthesis of new antitumor agents of potential clinical value.

The BALTIMORE CANCER RESEARCH CENTER conducts a collaborative integrated program of laboratory and clinical research in the therapy and management of cancer patients at the University of Maryland Hospital. The CLINICAL ONCOLOGY SECTION (Dr. Peter H. Wiernik, Head) provides complete medical care and treatment to patients with leukemia, lymphoma, and specific solid tumors utilizing combination chemotherapy in conjunction with surgery and radiotherapy. The NEUROSURGICAL BRAIN TUMOR PROGRAM is concerned with the diagnosis, operative intervention, and combined modality therapy of primary and secondary cancers of the central nervous system (Dr. Michael D. Walker, Head). A major microbiologic program (Dr. V. M. Young, Head) supports the infectious disease area, which includes the evaluation and use of protected patient environment employing the concept of laminar air flow. The patient care pharmacy, blood component replacement therapy program including leukocyte and platelet transfusion, clinical pharmacologic investigation of anticancer drugs, computer-oriented research programs in patient care, and extensive OPD round out the program. Certain aspects of the clinical program are collaborative endeavors between the University of Maryland Hospital and its multiple, fully approved residency training programs in major medical subspecialties. Training, which is provided in the clinical management of cancer patients, the performance of diagnostic procedures and their interpretation is accepted by the American Board of Internal Medicine toward boards in Internal Medicine and Medical Oncology.

The LABORATORY OF PHARMACOLOGY (Dr. Carl Levy, Chief) is concerned with basic and applied research programs in biochemical pharmacology, drug metabolism, molecular biology, cancer immunology, and metabolism. The SECTION OF BIOCHEMISTRY (Dr. Nicholas Bachur, Head) studies controls of cellular growth and differentiation and mechanisms for exogenous control (i.e., drugs). Particular interest is directed to clinical biochemical problems and problems of clinical pharmacology. The SECTION OF ENZYMOLOGY AND DRUG METABOLISM (DR. CARL LEVY, HEAD) STUDIES DRUG ENZYME INTERACTIONS IN A PROGRAM ATTEMPTING TO ELUCIDATE VARIOUS MARKERS OF CANCERS. IN ADDITION, THE SECTION is concerned with therapeutic agents affecting cellular proliferation characteristics. The SECTION OF IMMUNOLOGY AND CELL BIOLOGY (Dr. Michael R. Mardiney, Jr., Head) is involved with studying basic and applied aspects of host immune modulation with particular emphasis on cancer immunology. Programs involving the mechanism of adjuvant activity upon the immune response, as well as the development of techniques for monitoring host immunity to tumor are being carried out.

National Eye Institute

Carl Kupfer, M.D., Director

The National Eye Institute conducts, fosters, and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three Clinical Associates from those candidates who have completed an accredited 3-year ophthalmology program. Clinical Associates spend time in both clinical and laboratory research, including patient care activities.

In selection of Clinical and Research Associates, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

Laboratory and Clinical Research

The National Eye Institute has developed its clinical and research program into two major branches, the Laboratory of Vision Research and the Clinical Branch. The LABORATORY OF VISION RESEARCH plans and conducts fundamental laboratory research on the visual system. This includes anatomy, biochemistry, physiology, embryology, pharmacology, and experimental pathology of the visual system.

The CLINICAL BRANCH plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of disorders of the visual system. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the Clinical Branch's responsibility to investigate the causes and prevention of blindness. The major areas under study are cataracts of unusual origin, glaucoma, neuro-ophthalmology, ophthalmic genetics, vascular diseases, retinal degenerations, and ophthalmic pathology.

(1) Cataracts of unusual origin are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

(2) Neuro-ophthalmology: Patients from the ophthalmic and neurologic services are being studied using advanced methods for electro-oculography, pupillometry, video tape recording, and computer analysis. The main emphasis of these studies at present is on cerebellar disorders that affect ocular movements.

(3) Glaucoma: Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is underway.

Innovative surgical techniques are being assessed in selected cases of hemorrhage and congenital glaucoma and in cases in which anti-glaucoma surgery has failed.

Axoplasmic flow is being studied in optic nerves of glaucomatous monkeys and the properties of trabecular meshwork are being studied in tissue culture.

(4) Ophthalmic genetic studies include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogeneses of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

(5) In vascular diseases, investigations are being conducted to define underlying mechanisms in conditions such as diabetic retinopathy, macular degenerations, and other retinal vascular diseases or vascular disease of the optic nerve. A controlled clinical trial of anti-coagulation and thrombolytic agents in occlusion of the central retinal vein is underway.

(6) Ophthalmic Pathology: Eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied histopathologically and electron microscopically. Many of these eyes are from subjects who have rare or unusual metabolic diseases or who have been subjected to prolonged courses of anti-cancer treatment. There is opportunity for close collaboration with investigators in the laboratory for Vision Research in the Eye Institute.

The LABORATORY OF VISION RESEARCH is composed of the following disciplines:

(1) BIOCHEMISTRY. This section is conducting studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolisms of photoreceptors are also under investigation. Finally, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

(2) EXPERIMENTAL EMBRYOLOGY. The goals of this section are to identify and characterize the myriad tissue interaction that controls the orderly growth of the vertebrate eye and to assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the species and tissue specificities of these interactions, and the nature of these tissue interactions which control morphogenesis.

Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. In particular, attention is being focused on newly-discovered, cell-free, collagen containing "interior layers" that are transiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

(3) EXPERIMENTAL PATHOLOGY. Research being conducted in this section of the laboratory centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

(4) NEUROPHYSIOLOGY. Investigations in this section are currently underway to better understand the cellular organization underlying visual perception in both health and disease. Studies are being conducted on the responses of single nerve cells in the visual nervous system of the rhesus monkey. The purpose of this work is to understand how each nerve cell functions in contributing to visual sensations such as color, shape, movement, depth, etc. The technique employs fine glass micro-electrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an experimenter to observe the retina while stimulating it with punctate spots or lines of colored lights whose movement and shape can be quantitatively controlled. It requires electrophoresing particles of dye into single cells whose responses have been studied and then finding these particles precisely within the brain after the animal is sacrificed.

Studies in the rhesus monkey striate cortex, which have indicated that visual information processing by the brain involves feature detection rather than photographic reproduction, also include investigations of retinal function at the cellular level. The goal is to better understand vision and pathophysiology of retinal disease. Deeper understanding of abnormal states in the cellular physiology of the mammalian retina is also expected to emerge from studies in this section.

National Heart and Lung Institute

Jack Orloff, M.D., Director of Intramural Research

Frederic C. Bartter, M.D., Clinical Director

Associate Program in Medicine, Surgery, and the Basic Sciences

The National Heart and Lung Institute currently appoints three Research Associates and six Clinical Associates in Medicine for a 2-year period beginning each July 1. Several Staff Associates are also appointed in one or more of the Institute's laboratories. For those who are interested in lengthening their period of research experience, these appointments may usually be extended, by mutual agreement, for a third year. Four to five Clinical Associates are also appointed for 2-year periods in Surgery.

Research and Clinical Associates in Medicine

Candidates for Research and Clinical Associate positions have only one interview in the Heart and Lung Institute. Associates are interviewed by a committee made up of the Director of Intramural Research, the Clinical Director, and a Chief of one of the Institute's laboratories or branches. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the NHLI. After appointment and prior to entering on duty, each appointee will make a separate visit, at Institute expense, to select the laboratory in which to work. The choice is based on the background and interests of the Associate and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. (On the basis of past experience, it appears virtually certain that each Associate will be able to work with the group of his choice.) The level of research responsibility and freedom will depend upon his training and experience as well as his desires.

Each Associate in medicine will devote his time primarily to research in the laboratory under the immediate supervision of a preceptor in an area of his selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of his laboratory.

RESEARCH ASSOCIATE. These appointments are designed to give physicians an opportunity to improve their background for a career in basic medical research. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. No clinical assignments are involved (unless the Associate has chosen a laboratory involved directly in clinical investigation), but the Associates are welcome to attend any of the clinical teaching exercises.

CLINICAL ASSOCIATES. These appointments are designed to give physicians training in both clinical and basic research. Candidates must have completed a minimum of 1 year of internship plus 1 year of residency in internal medicine by the starting date of their appointment.

Clinical Associates will be responsible, under the guidance of investigators on the Heart and Lung Institute staff, for the medical care of patients during 10 of the first 12 months of their service. During this time they will rotate through the three medical services that serve the clinically oriented branches of the Heart and Lung Institute. These services occupy 75 beds and include: (1) Cardiology, (2) Endocrinology-Hypertension, and (3) Metabolism, Hematology and Lung.

The clinical period is one of intensive training under direction of the Clinical Director and staff. It offers exposure to case material of an extraordinary range and to highly sophisticated approaches to investigation of disease.

The Clinical Associate devotes both his time off the wards and a full 14 months of his 2-year assignment to laboratory research under direction of a preceptor *in any one of the Heart and Lung Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the optional third year for Associates who have chosen nonclinical laboratories.

STAFF ASSOCIATES. Laboratories within the Heart and Lung Institute sometimes have openings for Staff Associates appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Check List for the Institute. Selections for those positions are made by the Chief of the Laboratory. The position of Staff Associate is otherwise comparable to that of Research Associate.

CLINICAL ASSOCIATES IN SURGERY. The Surgery Branch of the National Heart and Lung Institute appoints four to five Associates in Surgery for a 2-year period beginning each July 1. The program is primarily designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in a research or academic atmosphere. Candidates must have completed an internship and at least 1 year of surgical residence by the starting date of their appointment.

STAFF ASSOCIATE IN EPIDEMIOLOGY. The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood, and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental, and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or one of the field programs. The Associateships may begin after internship or after 1 year of training in a clinical residency or school of public health. Candidates interested in this possibility are encouraged to write Dr. Manning Feinleib, Chief, Epidemiology Branch, National Heart and Lung Institute, Bethesda, Md. 20014, for more detailed information about specific assignments.

JOINT ENDOCRINOLOGY TRAINING PROGRAM. Clinical Associates from the National Heart and Lung Institute may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to qualify associates for the Endocrinology Subspecialty Boards. National Heart and Lung Institute participants will spend 6 months in full-time clinical activity consisting of 3 month rotations on the endocrine services of the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the Associate will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the Associate's 3 years will be spent primarily in research activity within the National Heart and Lung Institute, although he will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two Associates to enter this program in any one year.

Formal Instructions

The major form of didactic postgraduate instruction is through the evening courses offered by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Research, Clinical, and Staff Associates are expected to take advantage of this academic work.

Laboratories, Branches, and Sections

The laboratories, branches, and sections of the National Heart and Lung Institute, all of which are open to Clinical and Research Associates for their research work, are listed below with the names of their chiefs and a brief summary statement indicating the breadth of activities. Candidates desiring further information may obtain a current bibliography summarizing the activities of the current staff by writing to Dr. Jack Orloff, Director of Intramural Research, National Heart and Lung Institute, Bethesda, Md. 20014.

SECTION OF PATHOLOGY (Head, Dr. William C. Roberts). This section is concerned with the study of morphologic aspects of cardiovascular disease and their correlation with functional derangements. Morphologic analyses include electron microscopy.

SECTION ON THEORETICAL BIOPHYSICS (Head, Dr. John L. Stephenson). The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned both with the formulation of theoretical models and with the development of mathematical and computational methods for their analysis. Currently much of the research in the section centers on the mechanism of urine formation in the mammalian kidney.

LABORATORY OF BIOCHEMICAL GENETICS (Chief, Dr. Marshall Nirenberg).

SECTION ON MOLECULAR BIOLOGY (Head, Dr. Marshall Nirenberg). This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, i.e., genetic programs for differentiation that determine informational reactions of neuron. Systems and problems involve the culture of mammalian cells and hybrid cells, and gene function, for informational molecules, such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

SECTION ON MACROMOLECULES (Head, Dr. Alan Peterkofsky). Studies of regulatory mechanisms involved in nucleic acid and protein biochemistry. Current emphasis is on regulation of cyclic AMP metabolism in microbial systems as well as mammalian protein synthesis.

LABORATORY OF BIOCHEMISTRY (Chief, Dr. Earl R. Stadtman).

SECTION OF ENZYMES (Head, Dr. Earl R. Stadtman). Studies of diverse enzyme systems that offer unique opportunities to elucidate a number of basic biochemical phenomena, namely, those concerned with vitamin-coenzyme function, the cellular regulation of metabolism, the energy-dependent transport of metabolites across membrane barriers, and mechanisms of enzyme action.

SECTION IN INTERMEDIARY METABOLISM AND BIOENERGETICS (Head, Dr. Thressa C. Stadtman). This section is concerned primarily with investigations on the mechanisms of anaerobic amino acid dissimilation and phosphorylation coupled with anaerobic electron transfer processes. Special emphasis is on the roles of various coenzymes (*viz*, vitamin B_{12} coenzyme, CoA, pyridoxal phosphate, flavins, pyridine nucleotides, lipoic acid, and naphthoquinones) and of various electron transfer proteins (*viz*, selenoproteins, ferridoxins, flavoproteins and sulfhydryl proteins) in these processes.

SECTION ON PROTEIN CHEMISTRY (Head, Dr. Ann Ginsburg). Studies on protein structure are directed toward understanding protein-ligand interactions, protein-protein interactions, and enzyme catalysis and regulation.

LABORATORY OF CELL BIOLOGY (Chief, Dr. Edward D. Korn). This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

SECTION ON CELLULAR BIOCHEMISTRY AND ULTRASTRUCTURE (Head, Dr. Edward D. Korn). This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the biochemistry of the plasma membrane in relation to endocytosis and the molecular and ultrastructure basis of cell motility. Cytoplasmic actin, moyosin, and related proteins are purified and their interactions studied and compared to their muscle counterparts. Opportunities are available for research and training in biochemistry and electron microscopy.

SECTION ON CELLULAR PHYSIOLOGY (Acting Head, Dr. Evan Eisenberg). This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin and the troponins. Emphasis is on kinetic studies with pure proteins.

SECTION ON MEMBRANE ENZYMOLOGY (Head, Dr. Richard Hendler). This section studies enzyme systems that require organization on or interaction with membranes in order to insure their proper functioning. The synthesis of DNA by enzyme complexes and the electron transport chain of *E. Coli* are presently being investigated.

SECTION ON ORGANELLE BIOCHEMISTRY (Head, Dr. Martin Flavin). This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the physiological regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

LABORATORY OF CELLULAR METABOLISM (Chief, Dr. Martha Vaughn). Major areas of research interest are: (1) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides in regulation of growth and metabolism of mammalian cells grown in culture; and (2) elucidation of the means through which certain hormones and humoral agents (e.g., insulin, prostaglandins, adrenal steroids, kinins, biogenic amines) affect the formation, degradation and/or action of cyclic nucleotides in several types of mammalian cells.

LABORATORY OF CHEMICAL PHARMACOLOGY (Chief, Dr. James R. Gillette).

SECTION ON DRUG-ENZYME INTERACTION (Head, Dr. James R. Gillette). This section studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objective has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

SECTION ON PHYSIOLOGY (Head, Dr. Harriet M. Maling). This section studies interactions of drugs, particularly the mechanisms by which various treatments may alter the hepatotoxicity or pulmonary toxicity induced by various organic compounds. This includes study of how hepatotoxicity may be correlated with changes in the covalent binding of metabolites to liver lipids and proteins, changes in diene conjugation of microsomal lipids, and the formation of lipid peroxides, and effects on microsomal enzymes. The roles of endogenous mediators and autonomic and central nervous systems in the production of pulmonary edema and hindpaw inflammation are also under study.

SECTION ON CLINICAL PHARMACOLOGY (Head, Dr. Jerry R. Mitchell). Research centers around the isolation and identification of drugs, drug metabolites, and endogenous substances (steroids, prostaglandins, monoamines) from biological fluids, and the study of their rates of formation and disposition (pharmacokinetics). Additional studies examine the oxidative mechanisms by which monooxygenases or superoxide anion convert chemically stable drugs to highly reactive imidoquinones, free radicals, and other toxic electrophiles. Possible cause-effect relationships are examined between these determinants and drug-induced tissure lesions (e.g., acetaminophen, phenacetin, furosemide, isoniazid, or methyldopa hepatic and renal injury), drug therapy (e.g., propranolol concentrations and hypertension control), or disease processes (e.g., pathogenetic role of various steroids in low-renin hypertension). Routine procedures include chemical synthesis of radioactive stable-isotope analogs (e.g., for quantitative mass fragmentography), and drug analysis by t.l.c., g.c., l.c., mass spectrometry, or radioimmunoassay.

SECTION ON DRUG-TISSUE INTERACTION (Head, Dr. Gopal Krishna). This section is involved in the study of the initial events occurring in cells as the result of a variety of drug (hormone)-cell interactions. This section has been studying the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, it has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

LABORATORY OF CHEMISTRY (Chief, Dr. Henry M. Fales). Conducts research into methods for the structural analysis of organic compounds specifically *via* mass spectrometry, X-ray crystallography, nuclear magnetic resonance, etc., in addition to classical methods of chemical degradation. Also studies biosynthetic pathways *via* tracer techniques and chemical synthesis.

SECTION ON PHYSIOLOGICAL CHEMISTRY (Head, Dr. John I. Pisano). Normal and pathologic states in man are studied at the molecular level by advanced analytical techniques. Under investigation are the prostaglandins and vasoactive peptides (e.g., bradykinin and angiotensin), precursor proteins of the peptides and the enzymes involved in their biosynthesis and degradation. Research is currently directed to the study of hypertension, coagulation, and fibrinolysis.

LABORATORY OF EXPERIMENTAL ATHEROSCLEROSIS (Chief, Dr. Donald L. Fry). The laboratory program is directed toward experimental evaluation of the pathological, physiological, biophysical, chemical, and histological processes involved in the genesis of atherosclerosis. These studies are carried out with tissues from both animal colonies and human subjects.

SECTION ON VASCULAR PHYSIOLOGY (Head, Dr. Donald L. Fry). Studies the relationship of physical-chemical and hemodynamic forces to the processes of transvascular transport of atherogenic precursor molecules into the vascular tissue space and the response of the cellular and structural elements of the wall to these forces and substances.

SECTION ON COMPARATIVE ATHEROSCLEROSIS AND ARTERIAL METABOLISM (Head, Dr. Robert W. Mahley). Studies the origin and fate of plasma lipoproteins in experimental animals and man in relationship to arterial wall metabolism and atherosclerosis. Primary emphasis is on lipid and protein chemistry, response of arterial cells grown in tissue culture, and comparative atherosclerosis.

LABORATORY OF KIDNEY AND ELECTROLYTE METABOLISM (Chief, Dr. Maurice B. Burg).

SECTION ON ELECTROLYTE TRANSPORT (Head, Dr. Jack Orloff).

SECTION ON RENAL MECHANISMS (Head, Dr. Maurice B. Burg).

SECTION ON MEMBRANE METABOLISM (Head, Dr. Joseph S. Handler).

This laboratory conducts research on the mechanism and regulation (hormonal and otherwise) of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, toad bladder, and erythrocyte. Electrophysiology and intermediary metabolism as related to transport are emphasized.

LABORATORY OF TECHNICAL DEVELOPMENT (Chief, Dr. Robert L. Bowman). Conducts research into instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicro methods to practical clinical instrumentation.

SECTION ON PULMONARY AND CARDIAC ASSIST DEVICES (Head, Dr. Theodor Kolobow). Conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This program includes the development of improved blood oxygenators, blood pumps, and control systems.

CARDIOLOGY BRANCH (Chief, Dr. Stephen E. Epstein).

SECTION ON CARDIOVASCULAR DIAGNOSIS (Head, Dr. David R. Redwood). Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by heart failure.

SECTION ON CARDIOVASCULAR PHARMACOLOGY (Head, Dr. Stephen E. Epstein). Current work is concerned with a comprehensive study of the terminal nervous innervation of the heart and how it influences electrical stability of the ventricle. Cellular effects of drugs are also under investigation in isolated cardiac tissue. The action of antiarrhythmic agents under conditions of myocardial ischemia is under investigation.

SECTION ON CLINICAL PHYSIOLOGY (Head, Dr. Stephen E. Epstein). Research objectives are aimed towards an understanding of the physiologic, anatomic, and biochemical mechanisms responsible for control of the normal heart and circulation, an elucidation of the alterations produced by ischemic and nonischemic heart disease, and an evaluation of interventions designed to reverse the biochemical and thereby the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic and echocardiographic (one- and two-dimensional systems) studies in man, electron microscopic and biochemical studies of tissues obtained from human surgical specimens as well as from the experimental animal, and pharmacologic investigations in man and animals.

SECTION ON MOLECULAR CARDIOLOGY (Head, Dr. Robert S. Adelstein). Current investigations are directed toward an understanding of the function and control of the contractile proteins of heart, blood platelets and other cells (both muscle and nonmuscle). Projects include: (a) the role of cyclic AMP and phosphorylation in the regulation of contractile protein function, (b) the characterization, on a molecular level, of the contractile proteins found in disease states such as asymmetric septal hypertrophy (ASH) and those characterized by congestive failure.

Hypertension-Endocrine Branch (Chief, Dr. Frederic C. Bartter). This branch represents a merger of the previous Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension, but its activities are wide-ranging, as indicated by the description of section activities.

Section on Steroid and Mineral Metabolism (Head, Dr. Frederic C. Bartter). The principal research of this section is directed towards the pathophysiology of hypertension. It is broadly approached through clinical, physiological, and biochemical studies on steroid metabolism, on the renin-angiotensin system, on the kallikrein-kinin system, on the sympathetic nervous system, including catecholamines, on prostaglandins, and on the interrelations of each of the above with mineral metabolism and the kidney. Other research of this section involves the functions of the adrenal glands, the parathyroid glands, the pituitary glands, and their interrelationships with the kidneys, studies on metabolic bone disease and metabolism and on the pathogenesis of nephrolithiasis, and studies on a wide variety of other endocrine disorders. There is strong emphasis on chronobiology and chronopharmacology.

Section on Experimental Therapeutics (Head, Dr. Harry R. Keiser). A wide spectrum of research opportunities is offered, ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins and cathecholamines conducted both in man and in experimental animals. Other current studies encompass disorders of serotonin and histamine.

Section on Biochemical Pharmacology (Head, Dr. Walter M. Lovenberg). This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of the enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is a prime objective and investigations are extended from the molecular level to experimental animals and man.

Molecular Disease Branch (Acting Chief, Dr. Martha Vaughan). The activities of this branch are concerned primarily with the metabolism and transport of lipids. This includes the structure and relationships of lipoproteins and their apoprotein constituents, and the nature of enzymes involved in fat metabolism and the regulations of their activities, particularly as they control the concentrations of lipids in plasma and tissues. A major interest is dyslipoproteinemia and other metabolic diseases, especially those which are genetically determined, and related to lipid transport, metabolism and to atherosclerosis. The activities of the sections are integrated in such a way that, if they wish, associates may participate in collaborative work involving several sections.

SECTION ON PEPTIDE CHEMISTRY (Head, Dr. H. Bryan Brewer). Research is directed toward the analysis and synthesis of polypeptide hormones and lipoproteins with the object of developing knowledge of structure-function relationships.

SECTION ON LIPOPROTEIN STRUCTURE AND FUNCTIONS (Head, Dr. Peter Herbert). Research is concerned with isolation, identification, and structure of apolipoproteins, and elucidation of their special functions and interrelationships.

MOLECULAR HEMATOLOGY BRANCH (Chief, Dr. W. French Anderson). This branch is concerned with investigations into the mechanism and regulation of mammalian gene expression and protein synthesis, specifically relating to hemoglobin and to diseases involving the regulation of hemoglobin synthesis.

SECTION ON MOLECULAR GENETICS (Head, Dr. W. French Anderson). This section conducts investigations into the mechanism and regulation of hemoglobin biosynthesis. Studies include cell-free hemoglobin synthesis directed by isolated mRNA, purification and characterization of mammalian initiation and elongation factors, globin mRNA transcription from bone-marrow chromatin, and attempts to synthesize a DNA gene coding for globin mRNA with the use of the enzyme reverse transcriptase.

SECTION ON CLINICAL HEMATOLOGY (Head, Dr. Arthur W. Nienhuis). Application of the techniques of cell and molecular biology aimed at the understanding and treatment of human disorders of hemoglobin synthesis and erythroid differentiation. Major research areas include: the regulation of specific globin gene synthesis in differentiating erythroid cells *in vitro* and expression of globin genes in somatic cell hybrids. Patients with a broad range of red blood cell diseases are studied on the clinical service. Intracellular factors which influence the binding of oxygen to hemoglobin are being explored, particularly as they pertain to the deoxygenation and intracellular gelation of sickle hemoglobin. The value of iron chelation therapy in patients with transfusional hemosiderosis is under investigation.

PULMONARY BRANCH. RESEARCH IN THIS BRANCH IS DESIGNED TO APPROACH THE STRUCTURE AND FUNCTION OF RESPIRATORY TISSUE THROUGH MOLECULAR BIOLOGY. BOTH LABORATORY AND CLINICAL INVESTIGATIONS ARE CONDUCTED. THE LABORATORY PRESENTLY HAS TWO SECTIONS.

SECTION ON PULMONARY BIOCHEMISTRY (Head, Dr. Ronald Crystal). Investigation of the molecular basis of lung function in health and disease using techniques of molecular biology and tissue culture with specific emphasis on the regulation of synthesis and degradation of connective tissue elements. Clinical research is directed toward correlating physiologic, biochemical, and morphologic observations in patients with interstitial lung disease and patients with hereditary disorders of connective tissue.

SECTION ON MOLECULAR PHARMACOLOGY (Head, Dr. Elwood O. Titus). Studies the mechanisms by which neurohumoral transmitters, hormones, and drugs affect pulmonary and cardiovascular function. Activities include the characterization of cellular receptors for drugs and hormones, studies of the metabolism of biogenic amines in lung, and studies of the ionic mechanisms underlying signal transmission from nerve to muscle. Considerable emphasis is placed on the use of physical methods such as optical rotatory dispersion, fluorescence, nuclear magnetic resonance and electron spin resonance for the study of drug protein interactions.

SURGERY BRANCH (Chief, Dr. Andrew G. Morrow).

National Institute of Allergy and Infectious Diseases

John R. Seal, M.D., F.A.C.P., Scientific Director

Sheldon M. Wolff, M.D., F.A.C.P., Clinical Director

The NIAID annually appoints Associates for the laboratories described below. Clinical Associates are selected by the Clinical Director, are appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Research Associate appointments in the other laboratories may begin after internship or residency training. In general, those appointments which begin after 1 or more years of residency training have some degree of responsibility for human subjects in the research program but are not otherwise different from those which begin after internship.

Appointees through the Early Commissioning Program will be regarded as appointees through other programs and final identification as to positions for which they are being considered and as to whether or not the position will afford 1 or more years of residency training before entry will be made to prospective candidates at the time of interview.

Specific answers to any questions or additional information may be obtained by applicants from Dr. John R. Seal, Scientific Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. 20014. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests of applicant and information desired.

The LABORATORY OF CLINICAL INVESTIGATION (Sheldon M. Wolff, M.D., Chief).

The National Institute of Allergy and Infectious Diseases appoints six to eight Clinical Associates. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned clinical responsibilities are made during the second or third year except as dictated by the needs of the Clinical Associates' research.

There are 52 research beds. Clinical Associates consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each Clinical Associate selects his own area of investigative interest under the general preceptorship of the Clinical Director and the senior members of the staff of the Laboratory of Clinical Investigation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the Clinical Associate works, the subspecialty boards in infectious diseases or allergy will usually credit the training received towards admission to these board examinations.

Opportunities exist for research in a wide variety of areas of infectious and immunological disease. Examples of studies now in progress are:

- The etiology and pathogenesis of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- Pathogenesis of both experimental and clinical fevers.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The pathogenic mechanisms of the aspirin sensitivity-asthma syndromes.
- The structure and function of immunoglobulins of human and lower animal origin.
- The application of electron microscopy, autoradiographic, and cytochemical techniques to studies of cellular interactions in immunologic information processing both in humoral and cellular events.
- The interrelationship of coagulation and fibrinolysis to kinin generation and the role of these enzymatic pathways in the pathogenesis of reactions of the immediate hypersensitivity type.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Study of chronic bacterial pulmonary infections.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Dr. Sheldon M. Wolff.

Research Areas and Senior Staff
Allergic Diseases—Allen P. Kaplan, M.D.
Bacterial Diseases—Herbert Y. Reynolds, M.D.
Biologic Structure—Alan S. Rosenthal, M.D.
Clinical Allergy and Hypersensitivity—Charles H. Kirkpatrick, M.D.
Clinical Immunology—Michael M. Frank, M.D.
Clinical Mycology—John E. Bennett, M.D.
Clinical Parasitology—Franklin A. Neva, M.D.
Clinical Physiology—Anthony S. Fauci, M.D.

Medical Virology—Raphael Dolin, M.D.

The Laboratory of Viral Diseases (Wallace P. Rowe, M.D., Chief) conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses, and on host antiviral defense mechanisms.

Studies of tumor viruses are concentrated on murine leukemia viruses, adenovirus-SV40 hybrid viruses, and human papoviruses. These studies include investigations of the interactions between defective and competent viruses, the natural history and epidemiology of tumor viruses, genetic transmission of leukemia viruses in mice, and the viral and host genetic factors of importance in viral tumorigenesis.

The mechanism of action of interferon and inducers of interferon is studied by biological and biochemical approaches; the development and evaluation of new interferon inducers for possible clinical application are also undertaken.

Other areas of study are the biology of parvoviruses and the recently discovered viruses of certain medically important protozoa.

Research Areas and Senior Staff
- Cellular Virology—Kenneth K. Takemoto, Ph.D.
- Molecular Virology—Hilton B. Levy, Ph.D.
- Viral Oncology—Wallace P. Rowe, M.D.

The Laboratory of Biology of Viruses (Norman P. Salzman, Ph.D., Chief) is primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain specific antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for associates is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology and medicine.

Research Areas and Senior Staff
  Biochemical Virology—Norman P. Salzman, Ph.D.
  Macromolecular Biology—Bernard Moss, M.D., Ph.D.
  Molecular Structure—James A. Rose, M.D.
  Physical Biochemistry—Malcolm A. Martin, M.D.

The LABORATORY OF INFECTIOUS DISEASES (Robert M. Chanock, M.D., Chief) is concerned with the basic behavior of viral and mycoplasmal pathogens which play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as coronaviruses and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycroplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are made for 3 years.

Research Areas and Senior Staff
  Epidemiology—Albert Z. Kapikian, M.D.
  Hepatitis Virus—Robert H. Purcell, M.D.
  Mycoplasma—Joseph G. Tully, Ph.D.
  Respiratory Viruses—Robert M. Chanock, M.D.

The LABORATORY OF IMMUNOLOGY (William E. Paul, M.D., Chief) is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in both the prevention and pathogenesis of human diseases.

Areas of active investigation now include the study of the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells.

Further, active studies of the role of different lymphocyte classes in a variety of human diseases are underway and models for the study of the role of cellular immune responses in tumor immunity and for the investigation of immunotherapy of tumors are being developed.

Associates will have the opportunity to participate in studies in one (or more) of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff
  Cellular Immunity—Ira Green, M.D.; Ethan M. Shevach, M.D.
  Immunology—Donald E. Mosier, M.D., Ph.D.; William E. Paul, M.D.
  Immunochemistry—John K. Inman, Ph.D.
  Immunogenetics—Rose G. Mage, Ph.D.; Rose Lieberman
  Molecular Structure—Myron J. Waxdal, Ph.D.

The LABORATORY OF MICROBIAL IMMUNITY (Richard Asofsky, M.D., Chief) is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunological methods, offer the associate comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution, and susceptibility of the interacting components to various treatments which suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations. Autoimmune phenomena are studied using immune complex nephritis as a model. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The relationship of this disease to the presence and activity of such integrated viruses as the murine leukemia agents are studied. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff
  Biochemistry—Benjamin Prescott, Ph.D.
  Experimental Pathology—Richard Asofsky, M.D.
  Microbiology and Immunology—Phillip J. Baker, Ph.D.

The LABORATORY OF PARASITIC DISEASES (Franklin A. Neva, M.D., Chief) is engaged in both basic and applied studies of parasitic diseases of man. Basic research is conducted with a variety of parasites such as leishmania, trypansomes, malaria, amebae, toxoplasma, schistosomes, filaria, and tapeworms. Current studies include comparative mechanisms of energy transfer, non-heme iron respiratory proteins, ultrastructure of parasites, and in-vitro host-parasite interactions at the cellular level utilizing specialized optical techniques. Increasing emphasis is being devoted to consideration of immunologic response of the host in parasitic infections, both humoral and cellular. Some experimental infections of animals, such as malaria, leishmaniasis, and filariasis are utilized as models of naturally occurring disease in man. Availability of different species of simian parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate circumstances permit, certain problems are studied in the field in collaboration with local institutions. A Section of Clinical Parasitology is maintained within the Laboratory of Clinical Investigation providing a mutually useful opportunity for clinical studies.

The Pacific Research Section in Hawaii (under the direction of Dr. Leon Rosen) conducts research on vector-borne viral diseases as well as certain parasitic and other diseases of particular importance to the Pacific area. The isolated ecologic environment of the Pacific Islands is utilized for epidemiologic investigations. Current work is mainly on dengue hemorrhagic fever, swine influenza, and venereal diseases.

Within reasonable limits and with guidance of senior staff, associates can select their area of work and a preceptor. In addition, an organized program provides associates a broad exposure to medical parasitology including clinical aspects.

Research Areas and Senior Staff
- Cell Biology and Immunology—Harley G. Sheffield, Ph.D.
- Host-Parasite Relations—Allen W. Cheever, M.D.
- Malaria—Louis H. Miller, M.D.
- Parasitic and Vector-borne Viral Diseases, Pacific Area—Leon Rosen, M.D.
- Parasite Growth and Differentiation—Louis S. Diamond, Ph.D.
- Physiology and Biochemistry Section—Eugene C. Weinbach, Ph.D.

The LABORATORY OF STREPTOCOCCAL DISEASES (Roger M. Cole, Ph.D., M.D., Chief) investigates the genetics of streptococci and their bacteriophages, particularly in relation to ultrastructure, cell wall and surface composition, antigenic structure, competence, and autolytic enzymes. Current studies utilize phage-mediated transduction in group A streptococci; and transduction, DNA-mediated transformation and transfection, and lysogenization in group H streptococci. Efforts are directed to genetic transfer of natural characteristics (i.e., other than antibiotic resistance) which may alter epidemiological patterns in human disease. Emphasis is on surface antigens which can, if changed, result in differences in virulence, immunogenicity, phage susceptibility, adherence, and serologic recognition.

Other studies include virus-host reactions of newly-discovered viruses (phages) of some mycoplasmas; host-parasite interactions of gonococci; and the nature and role of cell wall and membrane components of staphylococci.

Associates have opportunities for training and experience in electron microscopy, microbial genetics, phage virology, and appropriate bacteriologic and biochemical methods related to the above or similar areas of investigation.

Research Areas and Senior Staff
- Streptococci and Bacteriophages—Roger M. Cole, Ph.D., M.D.
- Microbial Genetics—Jon M. Ranhand, Ph.D.
- Microbial Composition and Function—Eskin Huff, Ph.D.; Theodore S. Theodore, Ph.D.
- Microbial Ultrastructure—Roger M. Cole, Ph.D., M.D.

The ROCKY MOUNTAIN LABORATORY (Herbert G. Stoenner, D.V.M., Director) located at Hamilton, Mont., is internationally recognized for research on rickettsial and tick-borne diseases. The laboratory is a WHO Reference Center for Human Rickettsioses. In medical entomology and acarology, principal projects include biology and systematics of ticks and mites, ecology of selected tick- and mosquito-borne viruses, and general and subcellular relationships between arthropod-borne microbiota and their vectors as studied by various approaches, including arthropod tissue culture and electron microscopy.

Various aspects, particularly immunology and microbiology, of selected infectious diseases are under investigation. Scrapie and progressive pneumonia of sheep, and Aleutian disease and encephalopathy of mink are studied as models of chronic degenerative diseases of man. Limited studies are made on pertussis, rabies, tularemia, and the PTL group of organisms. More basic inquiries are made into fundamental mechanisms in delayed hypersensitive, cell-mediated immunity, and antibody production according to immunoglobulin class.

The fractionation of microbial agents, such as *Mycobacteria*, *Bordetella*, and Gram-negative organisms, by special biophysical and biochemical methods and the role of these subcellular fractions in immunity, hypersensitivity, tumor immunology, and other host responses are subjects of major investigations.

Opportunities for training associated with these research projects are provided in comparative pathology, electron microscopy, scanning electron microscopy, virology, immunology, immunochemistry, and a wide variety of specialized biophysical and biochemical methodology.

Research Areas and Senior Staff
- Allergy and Immunology—John J. Munoz, Ph.D.
- Slow Viral Diseases—William J. Hadlow, D.V.M.
- Epidemiology—Robert N. Philip, M.D.
- Medical Zoology and Zoonotic Diseases—J. Frederick Bell, M.D.

Molecular Biology—Edgar E. Ribi, Ph.D.
Rickettsial Diseases—Willy Burgdorfer, Ph.D.

National Institute of Arthritis, Metabolism and Digestive Diseases

J. E. Rall, M.D., Ph.D., Director of Intramural Research

Phillip Gorden, M.D., Clinical Director

Clinical Associates

The NIAMDD activates about 10 new Clinical Associates each year. The assignments are for 2 or 3 years and usually are not extended.

Each Clinical Associate is attached for his 2- or 3-year period to one of the clinical branches or sections, within which he carries out both clinical work and laboratory studies. He is, in effect, an apprentice clinical investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The Associate is encouraged to choose his own problem for independent investigation, subject to the limitation that the facilities required for its successful pursuit, and the technical advice and supervision necessary, must be available to the branch or section in which he is to be working. In addition, he provides professional care for the research patients admitted to the service of his branch chief, and assists in the work of that branch in the outpatient department. There is considerable variation among the branches of NIAMDD with respect to the proportion of the Associate's time required for patient care activities.

Clinical Associates of the Clinical Endocrinology, Diabetes, and Metabolic Diseases branches participate in a 3-year Inter-Institute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIAMDD Clinical Associates may also spend a third year in the Endocrinology Program.

Since appointments are for at least 2 years, vacancies do not necessarily occur within each program area each year. The chiefs of branches or sections having openings for new Clinical Associates, and the Clinical Director, screen applications and select candidates for personal interviews. After interviews are completed and the results of matching are announced, each successful candidate is asked to confirm his acceptance of the position with which he was matched. It is not possible, after this, to change the Associate's assignment within NIAMDD.

The list below identifies all of the clinical research branches within NIAMDD, and their sections, by title and by the name of the chief. The Program Area Selection Check List indicates those having vacancies to be filled at this time. Prospective applicants who are not familiar with the qualifications and research accomplishments of the branch and section chiefs, or with the details of their current investigative and clinical programs, are encouraged to write Dr. Phillip Gorden, Clinical Director, NIAMDD, Building 10, Room 9N–222, Bethesda, Md. 20014. Supplementary information sheets on each branch, together with selected bibliographic citations, are available on request.

Staff Associate in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment studying the epidemiology of chronic disease (diabetes, arthritis, cholelithiasis, etc.) among the Pima Indians of Arizona. In addition, clinical research opportunities are available in the Clinical Research Center of the Phoenix Indian Hospital. The Associateships begin after internship. Candidates interested in this possibility are encouraged to write Dr. Peter H. Bennett, Epidemiology & Field Studies Branch, NIAMDD, 1440 E. Indian School Road, Phoenix, Ariz. 85014, for more detailed information.

Research Associates

The National Institute of Arthritis, Metabolism, and Digestive Diseases has four positions available each year for Research Associates. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During his stay here, each Research Associate will devote the larger part of his time to participation in laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should he elect a clinical area, he would not participate in clinical care of patients. The Research Associate, approximately 1 year prior to beginning, will visit NIAMDD to select the laboratory and preceptor with whom he wishes to work. Candidates desiring further information about the laboratories, staff and bibliography of NIAMDD may obtain this by writing Dr. J. E. Rall, Director of Intramural Research, NIAMDD, National Institutes of Health, Bethesda, Md. 20014.

Clinical Research Branches

ARTHRITIS AND RHEUMATISM BRANCH—Dr. John L. Decker

Section on Connective Tissue Disease—Drs. John L. Decker, Paul Plotz, and Alfred D. Steinberg
Section on Human Biochemical Genetics—Dr. Elizabeth Neufeld
Section on Chemical Immunology—Dr. Henry Metzger

CLINICAL ENDOCRINOLOGY BRANCH—Dr. Jacob Robbins

Section on Endocrine Biochemistry—Drs. Jacob Robbins, Jan Wolff, Saul Rosen, Harold Edelhoch, Charles Lewallen, and Bruce Weintraub

CLINICAL HEMATOLOGY BRANCH—Dr. N. Raphael Shulman

DIABETES BRANCH—Drs. Jesse Roth, Phillip Gorden, Ronald Kahn, and Matthew Rechler

DIGESTIVE DISEASES BRANCH

Section on Gastroenterology—Drs. Jerry D. Gardner and Denis M. McCarthy
Section on Diseases of the Liver—Drs. Paul D. Berk and E. Anthony Jones
Section on Diseases of the American Indian—Dr. Peter H. Bennett, Acting

METABOLIC DISEASES BRANCH—Drs. Gerald D. Aurbach and Stephen Marx

PEDIATRIC METABOLISM BRANCH—Dr. Paul A. diSant'Agnese

Basic Research Laboratories

MATHEMATICAL RESEARCH BRANCH—Dr. John Z. Hearon

LABORATORY OF NUTRITION AND ENDOCRINOLOGY—Dr. Martin Rodbell

Section on Nutritional Biochemistry—Dr. John G. Bieri
Section on Endocrinology—Dr. Robert O. Scow
Section on Vitamin Metabolism—Dr. Bernard Kaufman
Section on Developmental Biochemistry—Dr. Robert T. Simpson
Section on Membrane Regulation—Dr. Martin Rodbell

LABORATORY OF BIOCHEMISTRY AND METABOLISM—Dr. G. Gilbert Ashwell

Section on Enzymes and Cellular Biochemistry—Dr. William B. Jakoby
Section on Intermediary Metabolism—Dr. Yale J. Topper

LABORATORY OF EXPERIMENTAL PATHOLOGY—Dr. Gert L. Laqueur

Section on Histochemistry—Dr. George G. Glenner
Section on Chemical Pathology—Dr. Robert Friedman
Section on Biophysical Histology—Dr. Ned Feder
Section on Cytogenics—Dr. J. H. Tjio

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Dr. Herbert Tabor

Section on Pharmacology—Dr. Herbert Tabor
Section on Biochemistry—Dr. Victor Ginsburg
Section on Biochemistry of Amino Acids—Dr. Simon Black
Section on Biochemistry of Cell Regulation—Dr. Leonard Kohn

LABORATORY OF CHEMISTRY—Dr. Bernhard Witkop

Section on Carbohydrates—Dr. C. Glaudemans
Section on Medicinal Chemistry—Dr. Everette L. May
Section on Biochemical Mechanisms—Dr. Louis A. Cohen
Section on Metabolites—Dr. Bernhard Witkop
Section on Microanalytical Services and Instrumentation—Dr. David Johnson
Section on Pharmacodynamics—Dr. John W. Daly

LABORATORY OF PHYSICAL BIOLOGY—Dr. Richard J. Podolsky

Section on Comparative Physiology—Dr. John B. Buck
Section on Cellular Physics—Dr. Richard J. Podolsky

LABORATORY OF CHEMICAL PHYSICS—Dr. Edwin D. Becker

Section on Molecular Biophysics—Dr. Edwin D. Becker
Section on Physiology—Dr. Paul Altland
Section on Spectroscopy and Structure—Dr. Elliot Charney
Section on Membrane Biophysics—Dr. William A. Hagins

LABORATORY OF MOLECULAR BIOLOGY—Dr. Terrell Hill

Section on Metabolic Enzymes—Dr. Martin Gellert
Section on Molecular Genetics—Dr. Jun-ichi Tomizawa
Section on Physical Chemistry—Dr. Gary Felsenfeld
Section on Molecular Structure—Dr. David R. Davies
Section on Microbial Genetics—Dr. Robert Martin
Section on Organic Chemistry—Dr. H. Todd Miles
Section on Theoretical Molecular Biology—Dr. Terrell Hill

LABORATORY OF CHEMICAL BIOLOGY—Dr. Christian B. Anfinsen

Section on Protein Chemistry—Dr. Christian B. Anfinsen
Section on Macromolecular Biology—Dr. Alan Schecter
Section on Protein Conformation—Dr. Hiroshi Taniuchi

LABORATORY OF BIOPHYSICAL CHEMISTRY—Dr. Koloman Laki

Section on Bioenergetics—Dr. David Kominz
Section on Macromolecules—Dr. Harry A. Saroff
Section on Physical Biochemistry—Dr. Koloman Laki

National Institute on Aging

Intramural Research Program

Nathan W. Shock, Ph.D., Acting Scientific Director

Reubin Andres, M.D., Acting Clinical Director

The Intramural Research Program of the National Institute on Aging is located at the Gerontology Research Center in Baltimore, Md.

The multidisciplinary program of the Center, located in a special research building on the campus of the Baltimore City Hospitals, offers Clinical (primarily clinical research) and Staff (primarily basic research) Associate training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, Associates may participate in clinical activities of the Baltimore City Hospitals and the nearby hospitals of the Johns Hopkins University and the University of Maryland. The Baltimore City Hospitals are affiliated with both institutions.

Associates participate in a seminar conducted by the staff of the Center which presents a comprehensive view of research in aging. Weekly research conferences are presented by members of the staff and invited lecturers.

In support of the programs the Center maintains extensive animal colonies to provide rats, mice, and house flies of known ages, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment. The library of the Center includes standard scientific journals as well as an extensive collection of the literature on aging research.

The Gerontology Research Center is composed of four branches:

LABORATORY OF CELLULAR AND COMPARATIVE PHYSIOLOGY (Takashi Makinodan, Ph.D., Chief). This laboratory is concerned with the effects of age on cellular differentiation in humans and other mammalian species. Currently, emphasis is placed on immunologic, biochemical, and genetic evaluations of cells of normal and genetically altered tissues.

Research in immunology (Takashi Makinodan, Ph.D., Albert A. Nordin, Ph.D., and William H. Adler, M.D., Program Coordinators) is focused on the nature, cause(s) and mechanism(s) of the decline with age in normal cell-mediated and humoral immune functions. Research has also been initiated for ways of replenishing the defective immune system of the aged and of controlling immunodepressed diseases prevalent among the aged.

Research in mammalian cell biology (Edward L. Schneider, M.D., Program Coordinator) is focused on metabolic and cellular changes associated with altered development and aging. Particular emphasis is placed on the relationship between altered nucleic acid and protein metabolic activities of cells and their chromosomal aberrations.

CLINICAL PHYSIOLOGY BRANCH (Reubin Andres, M.D., Chief). This branch is primarily concerned with studies on physiological changes occurring during the entire adult age span. Studies include quantitation of age changes, elucidation of mechanisms underlying these changes, and the relation between aging processes and specific disease states. Clinical research is conducted on 600 community-dwelling volunteers who comprise a panel for an extensive longitudinal study of human aging. They spend 2¾ days every 18 months on the Gerontology Research Ward in the adjoining Baltimore City Hospitals.

The ENDOCRINE SECTION (Robert I. Gregerman, M.D., Chief) conducts studies on (a) the enzymology and peptide chemistry of the reninangiotension system and (b) the influence of aging on hormonal responsiveness, especially as related to the adenylate cyclase mechanism.

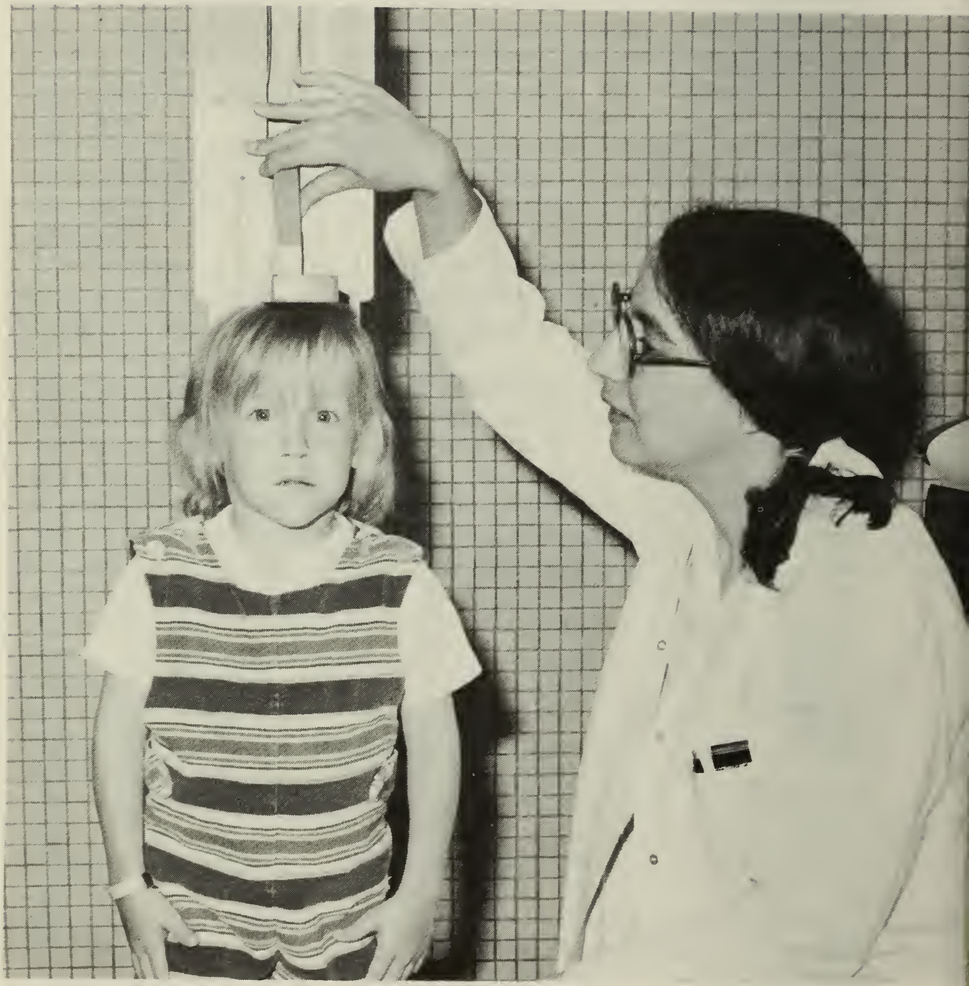
The CARDIOVASCULAR SECTION (Nathan W. Shock, Ph.D., Acting Chief) investigates cardiovascular hemodynamic function in man using noninvasive methods and in the rat and dog by a variety of experimental techniques.

The METABOLISM SECTION (Reubin Andres, M.D., Chief) conducts research on the kinetics of glucose homeostasis and related endocrine functions using a servo-control technique for clamping glucose levels in man.

The HUMAN PERFORMANCE SECTION (Arthur H. Norris, M.A., Chief). This section is responsible for a wide variety of studies on age changes in body composition, pulmonary and exercise physiology, and neuromuscular function.

LABORATORY OF BEHAVIORAL SCIENCES (Bernard T. Engel, Ph.D., Chief). This program includes studies of the effects of aging on motor behavior, perceptual skills, learning, memory, problem-solving ability, and personality characteristics. There are also studies on the interrelationships among aging and autonomic responses. The clinical applications of voluntary autonomic control are being investigated. Laboratory facilities exist for measuring cognitive and perceptual functions in man; psychophysiological responses in man; learning and motor behavior in rodents (including selected inbred strains of mice); learning, cardiovascular and neuropsychological responses in monkeys.

The LABORATORY OF MOLECULAR AGING (Bertram Sacktor, Ph.D., Chief) investigates mechanisms of the control of metabolism and of the expression of genetic information. The thrust of the research on metabolic processes is directed toward membrane biology. The problems and questions studied relate to: (1) the molecular organization of the membrane; (2) the role of the membrane in vectorial transport of small molecular species and proton-motive force; (3) the membranal reception of hormonal stimuli, the transduction and propagation of these stimuli; (4) the catalytic and integrative function of membranes; (5) the turnover of membranes; and (6) the failure to maintain membrane structure, leading to cell death. The thrust of the work on the propagation of genetic information is directed toward the interaction of metal ions with nucleic acids and proteins with the object of understanding these interactions in terms of biological function and particularly in the replication of DNA, transcription of RNA, and the synthesis of proteins.



National Institute of Child Health and Human Development

Intramural Research Program

James B. Sidbury, M.D., Scientific Director
Griff T. Ross, M.D., Ph.D. Clinical Director

The NICHD has 6-8 associate positions available each year. The appointments are for two or three years. The specific programs are indicated below. More detailed description of specific programs is available on request.

The Reproductive Research program is approved for accreditation by the endocrinology Boards. The Pregnancy Research Branch has a research program correlating the study of model systems with investigations of high risk pregnancies in patients. The pediatric component of the perinatal program includes developmental pharmacology, neonatology, and biochemical genetics. A new pediatric program is being established. The trainee who selects the pediatric program will rotate on the infant and children's wards, participating in clinical research programs as well as providing the care on those wards. During the first year he will select the laboratory he wishes to work in for the subsequent two years. This permits the trainee to select the laboratory experience after more knowledgeable exposure. Completion of the PL-2 pediatric experience is required.

The Behavioral Biology Branch (Phillip G. Nelson, M.D., Ph.D., Chief) conducts electrophysiologic and biochemical studies of the neurobiologic basis for short- and long-term interaction between nerve cells. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques. Combined molecular and behavior methods are used in the analysis of experiential modification of brain function.

The Section on Brain and Behavior (David Symmes, Ph.D., Head). Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed using microelectrode computer techniques. Behavioral consequences of brain lesions are studied.

The Section on Functional Neurochemistry (Harold Gainer, Ph.D., Head), conducts analysis of biochemical changes in identified neurons associated with electrophysiological and behavioral alterations. Specific neuronal protein synthesis and axoplasmic transport, glial-neuronal interactions, pacemaker activity, and neural peptides are studied.

The Section on Neurobiology (Phillip G. Nelson, M.D., Ph.D., Head). Tissue cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied electrophysiologically and biochemically. Long-term interactions between neurons and between nerve and muscle are of particular interest.

The LABORATORY OF BIOMEDICAL SCIENCES (J. C. ROBINSON, M.D., PH.D., CHIEF) CONDUCTS BASIC RESEARCH IN DEVELOPMENTAL ENZYMOLOGY, INTERMEDIARY METABOLISM, AND PHYSIOLOGICAL CONTROLS.

The SECTION ON DEVELOPMENTAL ENZYMOLOGY (J. C. ROBINSON, M.D., PH.D., CHIEF). PRIMARY INTEREST CENTERS ON THE IDENTIFICATION AND CHARACTERIZATION OF PREGNANCY-ASSOCIATED MATERNAL BLOOD PLASMA ENZYMES AND PROTEINS, THE CHARACTERIZATION OF ENZYMES SYNTHESIZED BY THE PLACENTA, AND AN ANALYSIS OF SOME OF THE FACTORS INVOLVED IN ENZYME INDUCTION IN THE DEVELOPING FETUS.

The SECTION ON PHYSIOLOGICAL CONTROLS (Walter H. Glinsmann, M.D., Chief) is concerned with hormonal, neurotransmitter, and substrate regulation of cell function and biochemical differentiation. Current studies focus on phosphoproteins controlling hepatic glucose output, substrate- and hormone-dependent induction of enzymes in embryonic and adult liver, mode of action of biogenic amines, and neuroendocrine regulation of indole metabolism in the pineal gland.

SECTION ON INTERMEDIARY METABOLISM (Gordon Guroff, Ph.D., Chief). This Section is involved in studies on the mechanism of action of enzymes of neurochemical interest, the biosynthesis and degradation of macromolecules in neural tissue, and the mechanism of action of nerve growth factor. Other studies concern the development of animal analogs of mental retardation through the use of specific chemical agents and enzyme inhibitors, the investigation of screening procedures for enzyme defects in mental retardation, and the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation. The overall efforts of the Section are to understand how changes in specific enzymes or growth factors lead to changes in the biochemical and behavioral patterns of the whole animal.

LABORATORY OF MOLECULAR GENETICS (Philip Leder, M.D., Chief) is concerned with the transfer and expression of genetic information. A wide variety of regulated biologic systems is under investigation, including models chosen from the areas of developmental biology, virology, cellular immunology, bacterial physiology, and bacteriophage genetics. At the present time, particular attention is being given to molecular aspects of the haematopoietic system, development of immunocompetency in cultured cells, differentiation of the embryonic chick lens, expression of the SV40 and adenovirus genomes and structural and physiologic aspects of certain RNA tumor viruses. In addition, studies in prokaryocytes are concerned with the mechanism and control of protein and RNA synthesis and with the replication and recombination of the bacteriophage lambda.

PERINATAL BIOLOGY PROGRAM consists of the Developmental Pharmacology Branch, Pregnancy Research Branch, and Neonatology Branch.

The DEVELOPMENTAL PHARMACOLOGY BRANCH (Daniel W. Nebert, M.D., Chief) investigates the molecular mechanisms underlying genetic differences and environmental factors influencing drug metabolism in man. This program complements and supports the ongoing Institute program in Perinatal Biology.

The SECTION ON PHARMACOGENETICS AND MOLECULAR TERATOLOGY (Daniel W. Nebert, M.D., Head). The primary interest centers around the development of methods *in vitro* and in cell culture for assessing and predicting teratogenic, mutagenic, or carcinogenic effects of exogenous or endogenous inducing compounds in animal model systems and in man. Developmental curves of drug-metabolizing enzymes and the transplacental inducing effect of drugs and environmental contaminants are investigated as possibly important factors in the etiology of birth defects.

The SECTION ON MOLECULAR TOXICOLOGY (Snorri S. Thorgeirsson, M.D., Ph.D., Head) conducts research on the mechanisms of toxicity and carcinogenicity caused by drugs and environmental chemicals. Repair mechanisms in mammalian cells following chemical or physical injury are also examined. The Section seeks to quantitate drug metabolism *in vitro* or in experimental animal model systems in order to develop techniques for predicting potentially toxic or carcinogenic reactions of drugs or chemicals in man.

PREGNANCY RESEARCH BRANCH (Ronald A. Chez, M.D., Chief) conducts research in the physiology of pregnancy, the effects of disease states on pregnancy, and the identification of those factors which increase perinatal and maternal morbidity and mortality. Extensive resources are available to study perinatal physiology and biochemistry in pregnant baboons, Rhesus monkeys, and sheep as models for human application. The interrelationships of fetal, placental, and maternal polypeptide hormone metabolism, tests of placental function and reserve, and the rate limiting influences on sex steroid production during pregnancy are presently being examined.

The clinical research program is directed at the management and care of pregnant patients both as inpatients and outpatients. Physicians interested in a career in academic medicine will have responsibility in both the clinical research and laboratory research areas. In addition, the opportunity to obtain experience in other disciplines represented at the National Institutes of Health is available on an individualized basis.

NEONATOLOGY BRANCH (Philip Farrell, M.D., Ph.D., Chief) consists of two sections, neonatology and biochemical genetics.

SECTION ON NEONATOLOGY (Dr. Philip Farrell, M.D., Ph.D., Head). This Section addresses nutritional studies of premature infants and small for dates infants. There is also research on lung lipid metabolism.

SECTION ON BIOCHEMICAL GENETICS (Joseph Schulman, M.D., Head). Infants and children with different inborn errors of metabolism are investigated, with emphasis on those affecting glutathione metabolism.

REPRODUCTION RESEARCH BRANCH (Griff Ross, M.D., Ph.D., Chief) conducts an integrated program of clinical, biochemical, and biologic studies pertinent to endocrinology and reproductive biology. The Branch accepts three Clinical Associates each year. During the first year, the associate will rotate among the Endocrinology Branches of the NIH to gain a broad knowledge of clinical endocrinology. The next two years are spent primarily in laboratory investigation in collaboration with a senior investigator.

The Branch staffs an Endocrinology Ward and Clinic with emphasis on problems involving the pituitary gland, adrenal cortex, gonads, growth and development. Infertility clinics for men and women are also sources of patients for clinical studies. The laboratory work ranges from studies of proteins and membranes to the physiology and biochemistry of steroid and polypeptide hormones.

SECTION OF HORMONAL REGULATION (Kevin J. Catt, M.D., Ph.D., Head) places emphasis on the binding and effects of polypeptide hormones such as gonadotropins and angiotensin. Major effects include characterization and isolation of membrane receptors and analysis of the receptor-second messenger systems.

TheSOCIAL AND BEHAVIORAL SCIENCES BRANCH (Leon J. Yarrow, Ph.D., Chief) engages in research on cognitive, social, and motivational development. Studies in progress have concentrated on the first year of life. Current investigations are concerned with both methodological and theoretical issues regarding early environmental influences, the assessment of neonatal characteristics and effectance motivation.

Among the problems studied are how specific aspects of maternal behavior affect cognitive growth, the development of effectance motivation, and the emergence of the special bond between mother and infant.

Research is underway on reciprocal influences in parent-infant interaction, e.g., the ways in which the infant's early characteristics affect both maternal and paternal behavior. A study is in progress on early father-infant interaction and the father's influence on the mother-infant relationship. A methodological study on the development and expression of attachment in several settings is being carried out.

National Institute of Dental Research

Wallace D. Armstrong, Ph.D., M.D.,
Acting Director of Intramural Research

Reuben P. Siraganian, M.D., Acting Clinical Director

The National Institute of Dental Research conducts research programs in laboratory, clinical and applied science, germane not only to dental health but also to the broader interests of biology and medicine.

Physicians are appointed for a 2-year period to the Institute's laboratory or clinical programs as Research or Clinical Associates. In general, three Research Associate and two Clinical Associate positions are available annually. Specific program areas, however, will not necessarily have vacancies for Associates in a particular year.

For the most part, dentists will be appointed for 2 years as Dental Clinical Associates, with a dual commitment to research and service as described on page 2. Dental graduates who possess specialized training and interests applicable to a particular research program of the Institute may also be considered for appointment as Staff Associates, with a full-time assignment to the appropriate laboratory or branch. The number of positions of this type to be filled will be determined solely according to programmatic need.

Minimum qualification for appointment as a Dental Clinical Associate is 1 year of accredited internship, or possession of equivalent advanced training beyond the dental degree. Dentists who have recently completed specialty training will be given particular consideration. Selection will usually be made one year prior to the effective date of appointment. Thus, for example, senior dental students who will enter an accredited internship July 1, 1976, are eligible to apply for an appointment commencing in 1977.

Brief descriptions of the program areas to which Associate appointments are made are provided in the following paragraphs. Additional information about specific programs may be obtained upon request to the Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, Md. 20014.

The LABORATORY OF BIOCHEMISTRY (Karl A. Piez, Ph.D., Chief) conducts programs in basic research covering a broad range of biochemical topics. The laboratory has as its objective the investigation of fundamental biochemical processes in normal and disease states.

There are two sections within the laboratory to which an Associate may be assigned.

The PROTEIN CHEMISTRY SECTION (Karl A. Piez, Ph.D., Chief) is concerned primarily with the chemistry and structure of collagen, elastin, and the carbohydrate components of connective tissue. Structure at the molecular level and the interactions that produce higher level tissue structure are determined by chemical, biophysical, and ultrastructure methods.

The ENZYME CHEMISTRY SECTION (John E. Folk, Ph.D., Chief) is studying the mechanism of action of enzymes using transglutaminases as models. These enzymes produce crosslinks in fibrin during blood clotting, in hair proteins, and in other biological situations. Protein chemical modification, synthesis of substrates, enzyme kinetics, and characterization of the products of crosslinking are used to elucidate the important aspects of enzyme structure and its relationship to catalytic activity.

The LABORATORY OF MICROBIOLOGY AND IMMUNOLOGY (Stephan E. Mergenhagen, Ph.D., Chief) has as its broad objective the elucidation of the role of microorganisms and immunological mechanisms in oral and systematic health and disease. The basic and clinical programs have application to medical and dental problems and cooperative research with other laboratories is conducted as required by the interdisciplinary nature of particular projects.

NIH Associates are assigned to one of four sections according to the interest of the candidate: Cellular Immunology (Joost J. Oppenheim, M.D., Chief), Humoral Immunity (Ann L. Sandberg, Ph.D., Chief), Clinical Immunology (Reuben P. Siraganian, M.D., Chief), or Microbiology (Charles L. Wittenberger, Ph.D., Chief).

Present projects in immunology encompass the roll of cell-mediated immunity, immune complexes and their effector systems (e.g., complement, vasoactive amines, lymphokines) in acute and chronic inflammatory reactions ultimately related to periodontal diseases, oral mucosal diseases, tissue transplantation, and autoimmune diseases. The microbiological programs include studies on microbial determinants of oral and systemic diseases, bacterial metabolism and its regulation, and taxonomy and ecology of the oral microbiota. Wherever possible fundamental approaches in these disciplines are translated into clinically-oriented or more applied projects through research protocols in clinical immunology as well as through collaboration with the National Caries Program of this Institute.

The LABORATORY OF BIOLOGICAL STRUCTURE (Marie U. Nylen, D.D.S., Chief) is primarily concerned with structural parameters of normal and abnormal function as expressed at varying levels of biological organization, ranging from the subcellular to the organismic. Information is adduced from the application of biophysical and chemical methods, techniques of experimental embryology, as well as from relevant tools of modern histology.

Research and Staff Associates are appointed to the Laboratory and are assigned by mutual agreement to a preceptor in the Molecular Structure Section (E. D. Eanes, Ph.D., Chief) or the Experimental Morphology Section (M. U. Nylen, D.D.S., Chief).

Currently the MOLECULAR STRUCTURE SECTION is engaged in studies on the crystal chemistry of calcium phosphates, the kinetics of mineral nucleation and crystal growth, calcification mechanisms, and the structural chemistry of mineralized matrices. The interests of the EXPERIMENTAL MORPHOLOGY SECTION are divided into two principal areas: (1) the growth and differentiation of mineralized tissues, normal as well as abnormal, and (2) the structure and function of exocrine glands with emphasis on the salivary glands. Opportunities for cooperative research and training are offered in electron microscopy and diffraction, contact and projection microradiography, x-ray diffraction, and infrared and Raman spectrophotometry.

The LABORATORY OF DEVELOPMENTAL BIOLOGY (George R. Martin, Ph.D., Chief) conducts research in (1) normal and abnormal tissue development, particularly craniofacial development and the etiology of anomalies, and (2) on the chemistry, biosynthesis and degradation of oral and other connective tissues.

The CONNECTIVE TISSUE SECTION (George R. Martin, Ph.D., Chief) conducts research on the formation and degradation of connective tissue with particular emphasis on developing structures. It relates the properties of these components to normal and pathological processes.

The CRANIOFACIAL ANOMALIES SECTION (C. T. G. King, Ph.D., Chief) conducts research on the normal development of the craniofacial region and develops animal models of anomalies induced either by genetic or by environmental manipulations, in order to delineate the etiology of the malformation.

The GENETICS AND EPIDEMIOLOGY SECTION (Jerry D. Niswander, D.D.S., Chief) conducts research on the occurrence, behavior, and consequences of normal and abnormal genetic traits with emphasis on oral-facial malformation and malocclusion in human populations and families. Activities include formulation of appropriate mathematical models and development of information concerning procedures appropriate for the control of genetic oral-facial disease and disorders at the population level.

The NEUROBIOLOGY AND ANESTHESIOLOGY BRANCH (Ronald Dubner, D.D.S., Ph.D., Chief) is concerned with the elucidation of basic mechanisms of oral-facial sensation with particular emphasis on pain sensation, and with the development and application of new methods of pain control. Fundamental research on peripheral and central nervous system mechanisms of oral-facial sensation is conducted by the NEURAL MECHANISMS SECTION (Ronald Dubner, D.D.S., Ph.D., Chief). The primary objective of this research group is to correlate behavioral responses to noxious and non-noxious thermal stimuli in monkey with neuronal structure and function at various levels of the trigeminal system. A multidisciplinary approach is employed and includes the following research activities: (1) electrophysiological studies of the response of single trigeminal nerve fibers and trigeminal brain stem neurons to the noxious and innocuous thermal and mechanical stimuli applied to the oral-facial region of monkeys; (2) neurocytological studies of the receptor, primary afferent, and brain stem organization of the trigeminal system in cat and monkey utilizing light- and electron-microscope techniques; and (3) behavior studies involving pain and temperature discrimination in monkeys trained to avoid potentially-noxious or noxious stimuli applied to the face. The NIDR Computer system is utilized for data analysis in the physiological experiments and will provide stimulus control in future behavioral and combined behavioral-electrophysiological experiments.

Applicants for positions in this section should have special training and experience in neurophysiology, neurocytology, experimental psychology, or computer technology.

Clinical research on the development and application of new methods of pain control is conducted by the ANESTHESIOLOGY SECTION (Edward J. Driscoll, D.D.S., Chief). The research objectives and activities of this group include: (1) physiological, pharmacological, and psychological studies of the effects and efficacy of new pharmacological agents utilized in the control of pain in ambulatory dental patients; (2) the development and evaluation of methods of measuring oral-facial pain threshold and tolerance levels; and (3) the development and application of behavioral and other non-pharmacological methods of pain control.

It would be advantageous for applicants for positions in this section to have some training and experience in anesthesiology, pharmacology or psychology.

The LABORATORY OF ORAL MEDICINE (Abner Louis Notkins, M.D., Chief) conducts basic and clinical research on diseases of the oral cavity. The program is highly interdisciplinary with emphasis on virology, oncology, and endocrinology. The staff includes people trained in medicine, dentistry, and the basic sciences. Present research projects include factors responsible for recurrent and persistent viral infections (e.g., herpes viruses), cellular immunity in viral infections, virus-induced immunopathology, the etiology of various dermatologic disorders including aphthous ulcers, and the role of viruses and other factors in diseases of the exocrine glands (e.g., Sjogren's syndrome, pancreatitis, salivary gland tumors) and endocrine glands (e.g., diabetes mellitus).

The CLINICAL INVESTIGATIONS BRANCH (Richard L. Webber, D.D.S., Ph.D., Chief) provides the specialty staff and associated resources for studies, both internally and externally initiated, which are of clinical interest and/or have an interface in the Dental Clinic. A broad spectrum of research activities are encompassed, ranging from theoretical analysis of factors influencing diagnosis and treatment of dental diseases to less sophisticated investigations such as the screening of clinic patients for specific potentially pathogenic microflora. The branch is uniquely suited to such a diverse range of activity by virtue of the wide variety of interests reflected among its dentist, physician, and allied health professional personnel. The availability of NIH-wide research patients from the Clinical Dental Services Section provides a pool of heterogeneous clinical material which is unique in its capacity for both retrospective and prospective control. Current research efforts are directed toward theoretical and applied studies which capitalize on this rare combination of resources.

The ORAL PHARYNGEAL DEVELOPMENT SECTION (James F. Bosma, M.D., Chief) is concerned with investigations of the development of form and of respiratory and feeding functions in normal and in impaired infants and children. Study methods commonly include standard and cephalometric roentgenography, cinephotography, and speech recording. Basic anatomic studies are an integral part of the work of this section. Particular efforts are made to adapt familiar study techniques and therapies to patients severely handicapped by anomaly or by neurologic impairment.

The Clinical Dental Services Section (William E. Wright, D.D.S., Chief) has as its prime function the dual responsibility of providing dental care to the NIH-wide research patient population as well as of providing facilities and supportive activity to all intra-Institute clinical programs. This patient exposure provides a unique opportunity for gaining experience in the observation, treatment, and study of orofacial problems related to a variety of systemic disease. All Dental Clinical Associates are assigned to this section administratively so as to facilitate their service-related activities. However, an individual program is arranged for each Associate in order that he may also pursue effectively his clinical and/or basic research interests. This section reports directly to the Clinical Director.

The Diagnostic Methodology Section (Richard L. Webber, D.D.S., Ph.D., Chief) undertakes a variety of research activities which include development of new diagnostic systems based on the application of specific analytical tools, including information theory, linear and nonlinear filter theory, signal detection theory, etc. In addition to determining the role played by analytical factors describing sources of diagnostic information, new methods of data acquisition and management are also under investigation. Opportunities for technically oriented associates of all types, therefore, exist within the multidisciplinary interface unique to this section.

Other related opportunities of a more general nature involve participation in the design and implementation of a variety of research protocols, wherein actual patients are studied on controlled bases to determine the effects of specific therapy on microbial flora and various disease processes.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D., Director

General

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biological factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods; the interaction of multiple agents resulting in enhanced effects; and the modifying effects of variable physical and biological states within man on susceptibility to and course of disease induced by these agents.

There is no single discipline that is unique or specific for the study of environmental health problems. Rather, the distinctive requirement for such research involves the application of a spectrum of skills including biology, biochemistry, bioengineering, biometry and epidemiology, chemistry, pathology, genetics, pharmacology, physics, toxicology, and veterinary sciences.

Location

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, N.C. The National Institute of Environmental Health Sciences is the only one of the 11 Institutes comprising the National Institutes of Health to be located away from the Bethesda, Md., campus.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University at Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, in seminars, and in other scientific and professional activities associated with the universities.

Staff Associates

Staff Associates will work at the National Institute of Environmental Health Sciences under the direction of Dr. David P. Rall, Director, and a Branch Chief in the Institute. Each Associate will work directly under a senior scientist in an area of research chosen by the Associate and the Institute.

The PHARMACOLOGY BRANCH (J. R. Fouts, Ph.D., Chief) studies the toxic effects on mammals of low level and/or chronic exposure to environmental constituents or contaminants. Interactions (upon or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently underway include: toxication-detoxication systems in liver, lung, and kidney and gut—effects of pollutants on these and the balance between toxication and detoxication reactions; age-related changes in detoxication systems in various organs; uptake, storage and release of chemicals in lung and liver; interaction of chemicals at sites of and kinetics of chemical distribution, storage and release—especially in the isolated perfused lung and liver, species differences in xenobiotic uptake and metabolism; marine pharmacology; inhalation toxicology—evaluation of toxicity of inhaled pesticides, solvents or aerosol spray constituents, interactions of inhaled chemicals; synthesis and release of lung lipids (surfactant and prostaglandins), incorporation of chemicals into tissue proteins and possible importance of these reactions to prolonged tissue storage or allergic reactions to chemicals; lung and cardiovascular function responses to inhaled chlorinated hydrocarbons; lung functions as detectors of inhalant toxicity; purification and comparison of components of toxication-detoxication systems in various organs.

Extensive interactions occur between Pharmacology and Toxicology and other branches; for example, in our program on pharmacokinetics (with Biometry), developmental pharmacology (with teratology and Environmental Toxicology) and inhalation toxicology (with Environmental Biology and Chemistry, Mutagenesis, and teratology). Interactions with Environmental Toxicology and Environmental Biology and Chemistry Branches are also involved in histologic, histopathologic, histochemical, and EM studies on tissues from exposed animals.

The ENVIRONMENTAL MUTAGENESIS BRANCH (Frederick J. de Serres, Ph.D., Chief) is responsible for the development of better methodology to test environmental chemical pollutants for mutagenic and carcinogenic activity as well as to monitor the human population to determine whether there is a change in the genetic load. In the first area, research currently underway includes investigation of the role of defective repair systems on inactivation and mutation-induction at specific gene loci, development of test systems in mammals to assay the effects of mutagens on the production of chromosome aberrations and gene mutations *in vitro* and *in vivo*, development of test systems to determine the genetic effect of airborne mutagens as well as the mutagenic effects of chemical carcinogens.

In the second area, method development is focused both on monitoring somatic mutations in peripheral blood cells and in skin fibroblasts, as well as on the detection and measurement of germinal mutations utilizing electrophoretic serum protein variants.

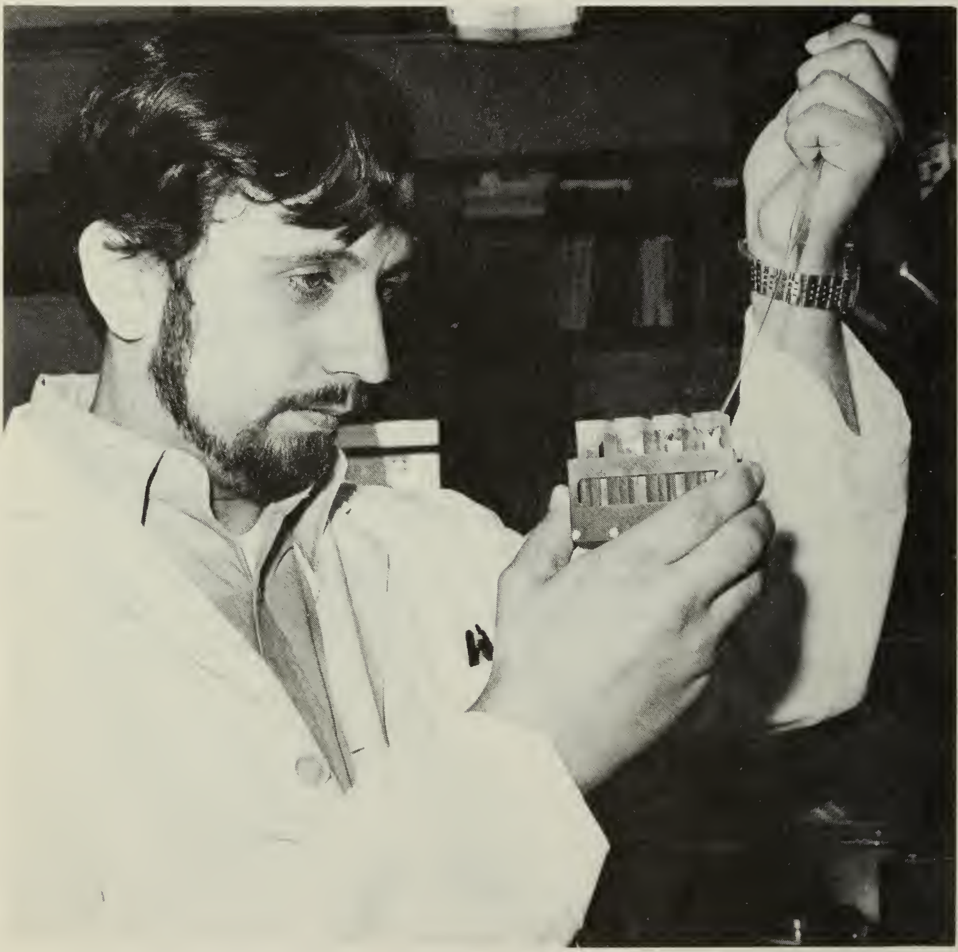
The techniques utilized in the investigations include: manipulation of mutagenic and carcinogenic agents, genetic analysis of microbial organisms, cytochemistry, mammalian tissue culture, autoradiography, cytogenetics, chromatography and ultracentrifugation, and electrophoresis.

The ENVIRONMENTAL TOXICOLOGY BRANCH (Robert L. Dixon, Ph.D., Chief). Scientific efforts of this Branch are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on environmental problems relating to reproduction and development. Toxicologic phenomena are studied from the descriptive to the molecular level in search of a better understanding of mechanisms. This increased understanding contributes to the development of better and more effective test procedures to predict toxicity in humans. Expertise is available in teratology, pharmacology, cell biology, and pathology. Test systems are likewise diverse and range from molecular biochemistry and electron microscopy through *in vitro* cell, organ, and embryo cultures to whole animals. Attempts are made to focus scientific resources on the following areas: environmental factors affecting germ cell development, teratology, transplacental toxicology, rapid toxicity test systems, biochemical toxicology and behavioral toxicology. Robert E. Staples, Ph.D., is Assistant Branch Chief for Teratology; George W. Lucier, Ph.D., is head of the Developmental Toxicology Section; and James S. Woods, Ph.D., is head of the Biochemical Toxicology Section. Individual efforts can be defined as study of the effects of foreign chemicals on oogenesis and ovarian function; passage of foreign chemicals into uterine luminal fluid and blastocyst; *in vitro* culture of mammalian gonadal tissues; DNA repair in mouse oocytes and zygotes; study of toxic actions and effects of environmental chemicals on spermatogenesis; DNA repair by teratogenicity of various environmental factors; comparison of local and systemic chemical treatment to induce teratogenic effects; evaluation of embryotoxicity; teratologic effects induced by heavy metals; low temperature storage of embryos and gametes; uterine luminal proteins and embryonic development; biochemical mechanisms related to the distribution and deleterious effects of environmental agents in developing systems; factors affecting metabolism and binding of hormones and foreign compounds during development; factors affecting hepatic heme synthesis and hematotoxicity during fetal mammalian development; and $(Na+ + K+)$ ATPase behavior and plasma membranal integrity in tissues of developing animals.

BIOMETRY BRANCH (David Hoel, Ph.D., Chief). The mission of the branch is to provide biometrical support for the NIEHS program by employing mathematical and statistical techniques to determine the biological effects of chemical, physical, and biological agents present in the environment. This is accomplished by incorporating in the Institute program statistical principles of experimental design, sampling, and data analysis for both laboratory and epidemiological studies, as well as mathematical analyses of biological systems. Mathematical and statistical procedures are applied and, when necessary, developed to determine the distribution and to estimate the rates of environmentally related diseases among populations, test hypotheses and study the interactions of environmental agents from multi-factor laboratory experiments, and develop mathematical models for describing and predicting biological responses to environmental agents. The branch provides computing services for the processing of large sets of data and for the analyses of complex problems. In order to accomplish the mission of the Biometry Branch the following areas of activity are identified: (a) Analytical Statistics, (b) Statistical Epidemiology, (c) Mathematical Statistics, (d) Biomathematics, (e) Computer Programming, and (f) Data Processing.

ENVIRONMENTAL BIOPHYSICS BRANCH (Lyle D. Thomas, Acting Chief) provides for NIEHS the capability of studying the impact of physical factors in the environment on man's health. Some activities are conducted in collaboration with or in response to specific requirements of other programs within the Institute. Activities of the branch include the investigation of the biological effects of physical factors alone or in combination with chemical and biological factors to which man may be exposed. Physical factors include but are not restricted to ionizing and non-ionizing radiation, heat, humidity, sound, and physical vibration. The branch is also responsible for the development and improvement of research instrumentation to support its own mission as well as the total NIEHS program.

The ENVIRONMENTAL BIOLOGY AND CHEMISTRY BRANCH (John A. Moore, D.V.M., Chief) is responsible for the acquisition, quarantine, husbandry, and veterinary care of all experimental colonies used at NIEHS; maintains collaborative support laboratories in the disciplines of Chemistry, Microbiology, Pathology, Histology and Electron Microscopy, and Veterinary Medicine; and plans and conducts research appropriate to the functions of branch laboratories. Current research programs include studies on the effect of environmental chemicals on immune competence; characterization of the toxic effect of the dibenzodioxins and dibenzofurans; investigation of a variety of environmental agents such as heavy metals; and electron mass spectrometry to detect metabolites.



National Institute of General Medical Sciences

Byron B. Clark, Ph.D., Director of the Pharmacology Research Associate Program

Pharmacology Research Associates

This Institute has eight to ten positions available each year for Pharmacology Research Associates. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of the National Institutes of Health, under the Pharmacology Research Associate Program.

The program is directed to those who have already made a commitment in pharmacology by training or research in the field.

Associates will study principles of pharmacology and toxicology and the application of physical and chemical concepts to pharmacology. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also available. During their tenure, Pharmacology Research Associates devote the larger portion of their time to laboratory research in the biomedical sciences, with no clinical responsibilities.

The objective of the Program is to develop leaders in pharmacology research for key positions in academic, industrial, and governmental research laboratories.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance both the work in progress and the competence of the prospective independent investigator. Preceptors and Research Associates are matched by a mutual selection procedure after personal interviews.

Associate candidates include those who will have received either the Ph.D. or M.D. degree and have research experience in pharmacology or toxicology. They may also include those with research experience in a related area but who wish to further their development in pharmacology. M.D. candidates may use this opportunity to further their training in basic pharmacological research in preparation for a career in clinical pharmacology or a related discipline. Each of the following Institutes of the National Institutes of Health participates in the Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

National Cancer Institute

LABORATORY OF CHEMICAL PHARMACOLOGY—Richard H. Adamson, Ph.D.

The general areas being studied include (1) the physiological disposition of antitumor agents; (2) structure-activity relationships (SAR) of antitumor agents; (3) new approaches to cancer chemotherapy and therapeutics in general, including studies with polymers and the nature of drug receptors; (4) comparative pharmacology; and (5) induction of tumors in nonhuman primates with carcinogens and/or virus and chemotherapy of these tumors.

LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY —David G. Jones, M.D., Ph.D.

Research is carried out on the pharmacology of cancer chemotherapeutics and related agents, and includes studies on the mode of action, physiological disposition and metabolism of this group of drugs. Of special concern are agents which act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the methotrexate; dihydrofolate reductase and 5-FdUMP: thymidylate synthetase interactions. Other areas of investigation include the role of enzyme induction in drug resistance; the effects of inhibition and enhancement of rates of drug metabolism on pharmacological activity; the physiological disposition of the rifampicin group of DNA- and RNA-polymerase inhibitors; and the role of the hepatic metalloflavoprotein aldehyde oxidase in the metabolism of N-heterocyclic compounds.

CHEMISTRY BRANCH—Harry V. Gelboin, Ph.D.

Research is being conducted on the molecular biology of microsomal enzyme regulation. Cell culture systems are used to study the mechanism of enzyme induction, the hydroxylation of polycyclic hydrocarbons, and the relationship of the microsomal enzyme system to drug action and carcinogenesis.

LABORATORY OF EXPERIMENTAL CHEMOTHERAPY—Abraham Goldin, Ph.D.

The program is concerned with the investigation of the mode of action of anticancer agents. Areas of investigation include: drug action in relation of cell cycle kinetics; metabolite-antimetabolite interrelationships in chemotherapy; combination chemotherapy with reference to drug potentiation and therapeutic synergism; adjuvant and immunochemotherapy; mechanisms and therapy of tumor cell resistance to drugs; tumor invasiveness and metastasis; structure-activity relationships of antitumor agents; chemotherapy of transplantable, carcinogen and viral induced, and spontaneous tumors; molecular biological and pharmacological investigation of the mechanism of action of antitumor agents. The laboratory program is closely related to clinical interests and an attempt is made to establish therapeutic principles for transference to clinical chemotherapy.

EXPERIMENTAL THERAPEUTICS PROGRAM—Vincent T. Oliverio, Ph.D.

Studies are generally related to the pharmacological disposition of antitumor agents and other drugs in man and animals through the use of established and newly developed analytical-biochemical techniques.

Particular emphasis is placed on the study of (a) the influence of simultaneously administered drugs on the distribution, protein binding, metabolism, renal clearance, and therapeutic activity of the individual agents, (b) the pharmacokinetics of the entry of drugs across membranes into sensitive and resistant tumor cells, and (c) the carcinogenic and other toxicological effects of drugs. Drugs of recent interest have been the folic acid antagonists, nitrosoalkylureas, substituted hydrazines, and plant alkaloids.

LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY—MARCO RABINOVITZ, PH.D.

Investigations in this laboratory are concerned with the characterization of structures and functions of cells which contribute to their resistance to selected cancer chemotherapeutic agents. Analytical procedures are devised to study sensitive and resistant cell lines with regard to receptor sites and agent metabolism. Such information permits the introduction of pharmacological and nutritional regimens to counteract or augment the observed sensitivity or resistance.

The laboratory operations include tissue culture, use of tumor-bearing animals, radioactive tracer techniques, and the synthesis of appropriately modified agents or synergists.

National Institute of Dental Research

LABORATORY OF DEVELOPMENTAL BIOLOGY AND ANOMALIES—Cecil T. G. King, Ph.D.

The section deals with the metabolism of drugs during gestation, placental transfer and how these drugs or their metabolites affect the developing embryo. Emphasis is placed on the oral facial region as it relates to the etiology of cleft palate formation and connective tissue disorders.

LABORATORY OF DEVELOPMENTAL BIOLOGY AND ANOMALIES—George R. Martin, Ph.D.

Individuals in this laboratory are studying the steps in normal and abnormal development. The Connective Tissue Section emphasizes studies on the formation of these tissues. The Section on Craniofacial Anomalies uses drug induced abnormalities to probe normal development.

National Institute of Mental Health

LABORATORY OF CLINICAL SCIENCE—Julius Axelrod, Ph.D.

The SECTION ON PHARMACOLOGY is engaged in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of drugs, biogenic amines, and enzymes; the distribution and metabolism of drugs, the isolation and characterization of enzymes involved in drug and biogenic amines metabolism. In addition, the laboratory is engaged in examining control mechanisms of the biochemistry of the pineal gland and biological rhythms.

LABORATORY OF CLINICAL SCIENCE—David M. Jacobowitz, Ph.D.

The SECTION ON HISTOPHARMACOLOGY is involved with studies of monominergic nerves (noradrenergic, dopaminergic, serotonergic) and cholinergic nerves in the brain and the peripheral autonomic nervous system. A multidisciplinary approach is used to correlate localization of central monominergic and cholinergic nerves with function. Histochemical, biochemical, and behavioral studies are currently underway. Using the catecholamine histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions is used to correlate changes in neuronal function with various parameters of behavior. Measurements of associated neuronal amines and enzymes are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a micropunch method and radioisotopic assays. Immunofluorescence methods are being used to study the localization of various enzymes in nerves. The growth of nerves is also studied using tissue and organ cultures.

LABORATORY OF PRECLINICAL PHARMACOLOGY—Erminio Costa, M.D.

This laboratory conducts a program of research in neurochemistry and neuropharmacology to elucidate the molecular nature of the mechanisms whereby various psychoactive drugs change neuronal function. Current research includes: (1) the nature of postjunctional receptors with particular regard to the biochemical reactions occurring at the neuroeffector junction in response to the release from nerve terminals of catecholamines, serotonin, GABA, acetylcholine, and substance "P"; (2) the molecular nature of short and long term regulation of rate-limiting enzymatic reactions controlling the dynamic equilibrium of neuronal monoamines at synapses; (3) the regulation of acetylcholine metabolism as it relates to changes in neuronal function; (4) the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin, and GABA by mass fragmentography in various brain nuclei; (5) the role of cyclases, phosphodiesterases and protein kinase translocation in the trans-synaptic regulation of protein synthesis in postsynaptic cells.

Laboratory of Neurochemistry—Seymour Kaufman, Ph.D.

The main effort of the laboratory is concerned with in-depth studies of a group of oxidative enzymes that catalyze key reactions in the nervous system. These enzymes include phenylalanine hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, and dopamine P-hydroxylase. The goal is to understand the mode of fetal development, the mechanism of action, the physical structure, and the regulatory properties of these enzymes. The interaction of the enzymes with other proteins, as well as with small molecules such as drugs and hormones, that can modulate their activities, is being studied. The regulatory properties of these enzymes are being examined at various levels of tissue organization, and include studies with highly purified enzymes as well as those with cell suspensions, tissue slices, and whole animals.

Laboratory of Clinical Science—Irwin J. Kopin, M.D.

The research efforts of the Section on Medicine are centered around the study of biochemical and physiological effects of drugs and toxins which alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes which control their synthesis in both the central and peripheral nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures.

Laboratory of Cerebral Metabolism—Louis Sokoloff, M.D.

The Laboratory of Cerebral Metabolism carries out a broad program of investigations on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the central nervous system. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones, which play important physiological roles in CNS function. Present emphasis is on the mechanism of action of thyroid hormones, not only on the maturation of the nervous system, but also on metabolic processes in all susceptible tissues. A method has recently been developed in this laboratory which permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiological and pathological states.

Laboratory of General and Comparative Biochemistry—Werner A. Klee, Ph.D.

The major emphasis of our current program is directed towards the elucidation of the mechanism of action of opiates and the peptides which normally interact with opiate receptors. Included in this program are studies on the isolation and characterization of opiate receptors, of endogenous morphine-like factors, and of the regulation of edenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in tissue culture, are aimed at understanding narcotic tolerance and dependence as well as analgesia and euphoria in biochemical terms. The relevance of this work to the action of other CNS active drugs and to normal brain function is also being explored.

Laboratory of Neuropharmacology—Barry J. Hoffer, M.D., Ph.D.

The section on developmental neurobiology conducts experiments on synaptic transmission and its maturation, with a particular emphasis on monoamine systems and cyclic nucleotides. The techniques used include electrophysiological recording, administration of drugs by superfusion and microiontophoresis, and histological and histochemical analysis. Studies are carried out on mature and developing central nervous regions *in situ*, as well as brain tissue transplanted to the anterior chamber of the eye.

Laboratory of Preclinical Pharmacology—N. H. Neff, Ph.D.

The section on biochemical pharmacology is concerned with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine containing neuron. Current studies are directed towards: (1) characterization of enzymes involved in amine metabolism; (2) biochemical evaluation of receptor responses; (3) evaluation of the mechanism of action of drugs that alter neuronal function; and (4) the possible role of the biogenic amines in various disease states.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Laboratory of Chemistry—John W. Daly, Ph.D.

The Section on Pharmacodynamics is engaged in research on the formation, degradation, and role of cyclic nucleotides in the central nervous system. The interrelationships between functional states of central neuronal networks and the responsiveness of cyclic nucleotide-generating systems to specific agents such as catecholamines, serotonin, histamine, adenosine, glutamate, GABA, etc.; the physiological role and mechanism of action of adenosine and membrane depolarization in regulation of cyclic AMP formation; and the morphological entities in brain slices associated with cyclic nucleotide formation in response to specific agents represent some aspects of this research.

Arthritis and Rheumatism Branch—Elizabeth Neufield, Ph.D.

Research is in the general area of human biochemical genetics, studied in cell culture. Of immediate interest are disorders of enzyme localization. For instance, in I-cell disease many hydrolytic enzymes are extracellular instead of intralysosomal. Such mutations lead to an understanding of the normal mechanism for packaging enzymes in their appropriate organelles.

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Herbert Tabor, M.D.

The work is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biological materials, and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Future work will be directed, in part, toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (e.g., enzyme characterization, bacteriophage, nucleic acid chemistry, isotopic and nonisotopic synthesis). The amino acid studies are concerned with the induced enzymes involved in histidine degradation, and their use as tools in studying induction, repression, and enzyme mechanisms. Other work in the laboratory includes studies on control mechanism for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability.

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Loretta Leive, Ph.D.

This laboratory investigates the structure, assembly, and function of membranes. One area of study is the mechanism whereby gram-negative organisms resist drugs that attack gram-positive organisms. It was found that the gram-negative outer membrane excludes these drugs, and that the lipopolysaccharide of the membrane participates in this barrier function. Treatments that increase permeability and mutants altered in outer membrane components or permeability are being used to analyze the mechanisms involved. This research may suggest ways of increasing drug sensitivity in gram-negative organisms. Another area of study concerns mechanisms by which membranes assemble. The outer membrane appears heterogeneous, with areas specialized for insertion of new molecules, and the rates and mechanisms of insertion and rearrangement are being studied. These studies, in a system susceptible to genetic manipulation and with a relatively simple membrane, may help elucidate such properties, which are basic to membranes in general.

National Heart and Lung Institute

MOLECULAR DISEASE BRANCH—W. French Anderson, M.D.

The SECTION ON MOLECULAR HEMATOLOGY investigates the mechanism and regulation of hemoglobin biosynthesis. Studies include the isolation and characterization of animal and human messenger RNA for hemoglobin, cell-free protein-synthesizing systems, the mechanism of initiation of protein synthesis, RNA transcription, cell fractionation, tissue culture of bone marrow cells, somatic cell hybridization, and patient investigations. Under direct investigation are the thalassemias, hemoglobinopathies, and other types of hemolytic anemias.

CARDIOLOGY BRANCH—Stephen E. Epstein, M.D.

The research objectives of this branch are oriented primarily toward an elucidation of the physiological and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacological interventions on the heart and peripheral circulation. Projects include pharmacologic, physiologic, and biochemical studies in man, intact animals, and smooth muscle cells grown in culture. Major emphasis is on the study of (1) the mechanisms responsible for arrhythmias and myocardial cell-death in acute myocardial infarction and their prevention, and (2) an understanding of the physiological and biochemical factors stimulating the atherosclerotic process.

LABORATORY OF CHEMICAL PHARMACOLOGY—James R. Gillette, Ph.D.

The SECTION ON DRUG-ENZYME INTERACTION studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objective has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal level.

HYPERTENSION-ENDOCRINE BRANCH—Walter Lovenberg, Ph.D.

The research of the SECTION ON BIOCHEMICAL PHARMACOLOGY is directed toward an understanding of mechanisms and regulation of monoamine neurotransmitter synthesis and the relationship of monoaminergic systems to specific diseases. Some of our current projects are: (1) molecular mechanisms of short- and long-term regulation of tyrosine hydroxylase activity; (2) chemical, structural and biosynthetic studies on dopamine-β-hydroxylase; (3) molecular events in the transduction of nerve impulses into changes in target cell proteins and enzyme levels; (4) the mechanism and regulation of serotonin synthesis in the CNS; (5) *in vivo* and *in vitro* studies on the mechanism of centrally active drugs; (6) the role of central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields including pharmacology, enzymology, protein chemistry, and molecular biology.

Laboratory of Biochemical Genetics—Marshall Nirenberg, Ph.D.

The Section on Molecular Biology is conducting studies on clonal cells derived from the nervous system including those that are of normal and neoplastic origin as well as somatic cell hybrids. The objectives are to identify the molecules and the reactions that enable cells to communicate with each other, via synaptic junctions, and to investigate the problem of how genes determine neuron sequence as neurons are assembled into circuits during embryonic development. Work would involve predominantly biochemistry, mammalian cell cultures, cyclic nucleotide enzymology, cell receptors, and enzymes of neurotransmitter metabolism.

Hypertension-Endocrine Branch—Harry R. Keiser, M.D.

The Section on Experimental Therapeutics offers a spectrum of research opportunity ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins, and catecholamines conducted both in man and in experimental animals. Other current studies encompass disorders of serotonin and histamine.

Laboratory of Biochemical Genetics—Alan Peterkofsky, Ph.D.

The Section on Macromolecules is currently concentrating on studies of cellular control mechanisms. The major focus of interest at present is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells. The current information suggests that cyclic AMP concentrations in *E. coli* are controlled by cellular metabolites by a mechanism similar in some respect to that by which hormones affect cyclic AMP levels in many mammalian cells. Another current area for study involves the mechanisms of some unusual aspects of protein synthesis in mammalian systems, e.g., N-terminal modification of immunoglobulins and/or albumin, as well as the biosynthesis of the tripeptide thyrotropin releasing factor.

Laboratory of Chemical Pharmacology—Jerry R. Mitchell, M.D., Ph.D.

Research in the Hypertension-Endocrine Branch centers around the isolation and identification of drugs, drug metabolites, and endogenous substances (steroids, prostaglandins, monoamines) from biological fluids, and the study of their rates of formation and disposition (pharmacokinetics). Additional studies examine the oxidative mechanisms by which monooxygenases or superoxide anion convert chemically stable drugs to highly reactive imidoquinones, free radicals, and other toxic electrophiles. Possible cause-effect relationships are examined between these determinants and drug-induced tissue lesions (e.g., acetaminophen, phenacetin, furosemide, isoniazid, or methyldopa hepatic and renal injury), drug therapy (e.g., propranolol concentrations and hypertension control), or disease processes (e.g., pathogenetic role of various steroids in low-renin hypertension). Routine procedures include chemical synthesis of radioactive and stable-isotope analogs (e.g., for quantitative mass fragmentography), and drug analysis by t.l.c., g.c., l.c., mass spectrometry or radioimmunoassay.

Pulmonary Branch—Elwood O. Titus, Ph.D.

The Section on Molecular Pharmacology studies those molecular changes in cell membranes which are associated with signal processing and regulation of cellular function, especially in vascular and pulmonary smooth muscle. Topographical or conformational changes associated with binding of drugs or humoral agents to individual proteins are measured by physical chemical techniques including electron spin resonance and nuclear magnetic resonance, circular dichroism, fluorescence spectroscopy, etc. Efforts to isolate receptor substances are carried out. Some work on the pharmacology of isolated tissues is performed as needed for correlation of physiological effects with changes in membrane chemistry. Current studies deal largely with the role of conformationally mobile sites on membrane proteins in regulation of ion transport by steroidal drugs. Affinity labels and double isotope procedures are used to characterize such sites on $Na^{+} + K^{+}$—dependent transport ATPase and also to characterize peripheral adrenergic receptors.

Pulmonary Branch—Michael A. Beaven, Ph.D.

The Section on Molecular Pharmacology has a broad interest in the biogenic amines (histamine, serotonin, and the catecholamines), the polyamines (putrescine, spermine, and spermidine), and the enzymes involved in the synthesis and degradation of these amines. The work is concerned with the role of these amines in health and disease. Investigations have included: (1) the study of polyamines in tissues with rapid cell turnover, e.g., thymus lymphocytes, regenerating liver, and various tumors; (2) the release and synthesis of histamine, serotonin, and other tissue factors in inflammatory and allergic reactions in *in vivo* and *in vitro* systems; and (3) alterations in amine metabolism produced by drug treatment; e.g., the effect of aspirin on histamine metabolism. Current studies are directed toward the role of biogenic amines in lung and include investigations of the influence of age, infection, and allergic conditions on the synthesis and turnover of histamine and serotonin in lung. Normal and germ-free animals are being used for these studies. The work requires the use of sensitive isotopic assay procedures and particular emphasis is given to the possible use of these procedures in the diagnosis of disease.

PULMONARY BRANCH—Colin F. Chignell, Ph.D.

The SECTION ON MOLECULAR PHARMACOLOGY is concerned with the mechanism of drug action at the molecular level. Drug interactions with biological systems are being studied with a variety of physical and spectroscopic techniques including ultraviolet and visible absorption spectroscopy, nuclear magnetic resonance and electron spin resonance (including the use of spin labels), and optical rotatory dispersion and circular dichroism. Current areas of active research include the binding of drugs to plasma proteins, nucleic acids, membranes, and other cellular components, the binding of colchicine and its analogs to microtubule protein, the interaction of decamethonium and hexamethonium with acetylcholinesterase and acetylcholine receptor protein from *Torpedo californica*, and the inhibition of mammalian erythrocyte carbonic anhydrase by aromatic sulfonamides. Other projects are concerned with the mechanism of drug-induced phototoxicity and photoallergy and the characterization of lung surfactant lipoprotein.

LABORATORY OF CELLULAR METABOLISM—Martha Vaughan, M.D.

Major areas of research interest are (1) the mechanisms underlying hormonal control of lipolysis in fat cells, with emphasis at present on characterization of the hormone-sensitive lipase and elucidation of manner in which insulin, prostaglandins, and adrenal steroids affect the formation, degradation, and action of cyclic AMP, and (2) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides (e.g., prostaglandins, adrenal steroids) in regulation of growth and morphology of mammalian cells grown in culture, and (3) the nature and regulation of guanylate cyclases in smooth muscle and other cells.

National Institute of Allergy and Infectious Diseases

LABORATORY OF PARASITIC DISEASES—Eugene Weinbach, Ph.D.

The effects of drugs and other toxic agents on the metabolism of mitochondria are studied to provide a biochemical basis for their pharmacological activity. Current studies are concerned with electron transport, oxidative phosphorylation, ion translocation, and structure-function relationships in mitochondria. Particular attention has been given to compounds that uncouple oxidative phosphorylation and to their mechanism of action. A hypothesis concerning the mechanism of uncoupling of oxidative phosphorylation based on conformational changes in proteins involved in energy conservation has been derived from these studies. The work will be extended to determine if other pharmacologically active agents induce conformational changes in proteins and thereby alter their catalytic function.

National Institute of Child Health and Human Development

LABORATORY OF BIOMEDICAL SCIENCES—David C. Klein, Ph.D.

Investigations within the SECTION ON PHYSIOLOGICAL CONTROLS have focused on describing the molecular mechanisms through which hormones and biogenic amines regulate gene expression. The role of cyclic AMP in the regulation of the activity of enzymes and the regulation of indole metabolism has been one of the major areas of interest. Current research is concerned with the relationship between biogenic amines and the production and release of peptide hormones from neuroendocrine tissue. In addition, enzyme induction is being studied using biochemical and electrophysiological tools to understand the relationship between the biochemical and electrophysiological effects of neurotransmitters.

BEHAVIORAL BIOLOGY BRANCH—Phillip G. Nelson, M.D., Ph.D.

The BEHAVIORAL BIOLOGY BRANCH conducts research in neurobiology using tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress.

DEVELOPMENTAL PHARMACOLOGY BRANCH—Daniel W. Nebert, M.D.

This branch investigates the molecular mechanisms underlying genetic differences and environmental factors influencing drug metabolism in man. The program includes a search to understand congenital malformations, the toxic or mutagenic or carcinogenic effect of drugs, the development of drug-metabolizing enzymes and their capacity to be induced or repressed, and jaundice caused by breast milk feeding. Genetics in mice and cell culture techniques are commonly used as experimental model systems. Attempts are being made to distinguish genetic factors from environmental influences and to develop methods for assessing or predicting a compound's teratogenic, toxic, mutagenic, or carcinogenic effect in man. This research complements and supports the on-going Institute programs in the Pregnancy Research Branch and the Neonatal and Pediatric Medicine Branch. Intent is to form an overall Perinatal Biology Program which will span the health concerns of children and mothers during both the prenatal and postnatal periods.

National Institute of Environmental Health Sciences

Pharmacology Branch—James R. Fouts, Ph.D.

Research Programs: Inhalation Toxicology - exposures of animals to various mixtures of vapors, aerosols, particles, etc., and evaluation of mechanisms of damage, especially to the lung. *Pulmonary Group* - use of isolated perfused lung in study of chemical uptake and effect of chemicals on nonrespiratory functions, lung physiology, and biochemistry. Collaboration with clinical groups at Duke University on chemical-induced lung disease. *Pharmacokinetics* - whole animal and isolated organ studies of rates and mechanisms of chemical uptake, storage, and release. Collaboration with DCRT, NCI groups in Bethesda. *Marine Pharmacology* - studies of mechanisms of pollutant accumulation in edible marine species; use of marine systems to detect waterborne pollutants. Field labs in Maine and Florida; interagency collaborative efforts, collaboration with university scientists here at NIEHS as well as in Maine and Florida. *Toxication-Detoxication* - toxication-detoxication systems in hepatic versus extra-hepatic tissues, species differences, developmental patterns; role of metabolic activation of chemicals in mutagenesis, teratology.

Environmental Toxicology Branch—Robert L. Dixon, Ph.D.

The scientific efforts of this branch are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on environmental problems relating to reproduction and development. Toxicologic phenomena are studied from the descriptive to the molecular level in search of a better understanding of mechanisms. This increased understanding contributes to the development of better and more effective test procedures to predict toxicity in humans. Test systems are diverse and range from molecular biochemistry and electron microscopy, through *in vitro* cell, organ, and embryo cultures, to whole animals. Specific project areas include the following: (1) Mechanisms of abnormal embryonic development (teratology; transplacental toxicology), (2) Perinatal enzymology and immunology (biochemical indicators of developmental toxicology), (3) Mechanisms and toxicity of hormonally active chemicals, and (4) Gene expression and macromolecular synthesis during embryonic development.

The Pharmacology Research Associate Committee

Choice of program area depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. The Pharmacology

Research Associate Committee offers counseling to applicants invited to the NIH for interviews.

National Institute of Mental Health

John C. Eberhart, Ph.D., Director of Intramural Research

Robert A. Cohen, M.D., Ph.D., Director,
Division of Clinical and Behavioral Research

This Institute offers an opportunity for postdoctoral research training in psychiatry and in the biological and behavioral sciences. Clinical Associates are assigned clinical responsibility in caring for patients who are admitted for both therapeutic and research purposes. Staff Associates engage in laboratory research in one of the biological or behavioral science laboratories under the preceptorship of one of the senior staff, and may in addition participate in tutorial seminars and other teaching programs, as their needs and desires indicate. After reporting for duty certain Staff Associates who have particular need for and interest in the tutorial seminar program, and whose qualifications are high, may be designated as Research Associates, and will be given priority in admission to the seminar programs.

Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all Associates to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Descriptions of the NIMH program areas to which Associates will be appointed follow.

The ADULT PSYCHIATRY BRANCH (W. E. Bunney, Jr., M.D., Chief; Senior Staff: Dr. G. L. Brown, Dr. M. Buchsbaum, Dr. E. Gershon, Dr. C. Gillin, Dr. R. M. Post, Dr. D. P. van Kammen, and Dr. R. Wyatt) conducts a broad program of research and training in clinical and biological aspects of psychiatry, including psychological, genetic, pharmacological, and biochemical investigations of depression, and schizophrenia and childhood mental illness. Ordinarily, 2 years of clinical psychiatric residency training should precede arrival on duty; for Clinical Associates, the program is accredited for third-year psychiatric residency training. Current research projects include: (1) assessment, treatment, and followup of acute psychotic patients and their families; (2) biological correlates (sleep, activity, biogenic amines and related enzymes, and endocrine function) in acute schizophrenic, manic-depressive, drug-induced psychoses, and childhood mental illness; (3) mechanisms of action of psychotropic and addictive drugs; (4) clinical assessment of new psychotherapeutic drugs and treatment modalities such as acupuncture; (5) genetic studies of biological, pharmacological, and personality characteristics of patients with affective disorders and their relatives, and development of models of genetic transmission of affective disorders; (6) perceptual psychophysiology information theory and attention using computer and averaged evoked potential techniques; (7) investigation of behavioral pharmacology, models of depression and schizophrenia, CNS and spinal fluid physiology and biochemistry in subhuman primates; (8) studies of the physiology, biochemistry, and pharmacology of receptor function in animals and man.

The LABORATORY OF CLINICAL SCIENCE (Irwin J. Kopin, M.D., Chief; Senior Staff: Dr. Julius Axelrod, Dr. Michael H. Ebert, Dr. Frederick K. Goodwin, Dr. David M. Jacobowitz, and Dr. Dennis Murphy) conducts a program of research in biochemistry, pharmacology, physiology, medicine, and psychiatry and the interrelationships between them. Current research includes: (1) mechanism of action and metabolism of drugs and hormones which act in the nervous system; (2) biochemical studies in endocrine and metabolic disorders of amino acids, catecholamines, and other biogenic amines; (3) clinical pharmacology including drug metabolism; (4) longitudinal investigation of patients (acute or episodic psychosis, depression) stressing biological factors (endocrine function, catecholamines, serum proteins, specific enzyme activities); (5) biological rhythms and their control; (6) biological aspects of toxic psychoses and drug addiction; and (7) relationship of biogenic amines to neuropsychiatric disorders.

The LABORATORY OF NEUROBIOLOGY (Ichiji Tasaki, M.D., Chief; Senior Staff: Robert H. Wurtz, Ph.D.) conducts research on the nervous system at several levels ranging from biochemical and biophysical studies of single excitable cells to studies of systems of neurons in the brain. Current research projects include studies on: (1) the excitation process in nerve and muscle membrane using recently developed optical techniques to demonstrate changes in birefringence, turbidity, and fluorescence in excitable tissue during an action potential; (2) biophysics of model membrane systems; and (3) the integration in the brain of visual information and extravisual input (such as eye movements and attention) using single unit recording in awake monkeys performing a learned task.

The LABORATORY OF GENERAL AND COMPARATIVE BIOCHEMISTRY (Giulio L. Cantoni, M.D., Chief; Senior Staff: Werner A. Klee, Ph.D., Carl R. Merril, M.D., Stuart H. Mudd, M.D.) conducts investigations on: Mechanisms and pathways of protein biosynthesis; biological methylations; alkaloid biosynthesis; differentiation and gene expression in eukaryotes.

The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, RNAse action, mechanism of drug addiction, muscle differentiation in cell culture, and transgenosis.

The SECTION ON ALKALOID BIOSYNTHESIS studies the enzymes involved in alkaloid biosynthesis, their control and biosynthesis in relation to morphogenetic development of the plant; also, enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

The LABORATORY OF CEREBRAL METABOLISM (Louis Sokoloff, M.D., Chief; Senior Staff: Dr. Marian W. Kies, Dr. Russell E. Martenson, Dr. Elaine E. Kaufman, and Dr. Charles Kennedy) conducts a program of research on: (1) biochemical and immunochemical studies on myelin and characterization of CNS proteins and their relationship in autosensitization reactions of the CNS; (2) biochemistry of the developing nervous system; (3) effects of thyroxine and other hormones on protein synthesis and on the development of the nervous system; and (4) regional cerebral blood flow and glucose consumption and physiological environmental factors which influence them during development of the nervous system.

The LABORATORY OF NEUROCHEMISTRY (Seymour Kaufman, Ph.D., Chief; Senior Staff: Dr. Howard A. Nash, Dr. David M. Neville, Jr., and Dr. Audrey L. Stone) conducts investigations in the following areas: (1) the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine hydroxylating system. In addition to studies with the pure enzymes, there is emphasis on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia; (2) the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin and the relationship between the properties of the enzymes and physiological regulation of rates of synthesis of these neurotransmitters; (3) the biochemical basis for skeletal muscle hypertrophy including the effects of exercise and neural factors in the process; (4) cell surface membrane proteins and receptors in their role in cellular differentiation; and (5) the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

The LABORATORY OF NEUROPHYSIOLOGY (E. V. Evarts, M.D., Chief; Senior Staff: Frederick A. Miles, Ph.D. and Stanley I. Rapoport, M.D.) conducts research on (1) neural control of movement; (2) plasticity of stimulus-response relations; (3) the physiology and pharmacology of the blood-brain barrier; and (4) metabolic correlates of brain activity.

The studies on neural control of movement are designed to elucidate the functional interrelations between motor subsystems (e.g., spinal cord, brain stem, cerebellum, basal ganglia, thalamus, and cerebral cortex). This work involves behavioral, electrophysiological, and neuroanatomical techniques. Projects are aimed at understanding both reflex and voluntary motor function. Studies on control of eye movements focus both on the vestibulo-ocular reflex and on saccadic movements. Discharges of single nerve cells are recorded with microelectrodes in monkeys trained to carry out movements, and the results are interpreted in relation to the anatomical input-output properties of the loci from which recordings are obtained.

Work in the area of plasticity of stimulus-response relations involves: the role of segmental and suprasegmental neural factors in determining the modifications of muscular activity associated with motor learning in man and subhuman primates. Studies also focus on mechanisms underlying adaptive changes in the vestibulo-ocular reflex in the monkey.

The blood-brain barrier, which regulates cerebral metabolism and function, is opened reversibly for experimental pharmacology, its structure at cerebral blood vessels is elucidated with electron microscopy, and the principles regulating transport are determined by experimental and theoretical means.

Increased neuronal activity is associated with increased neuronal metabolism, and techniques for detecting localized changes in cerebral metabolism are now being used to discover the location and magnitude of metabolic changes associated with a variety of different cerebral functional states. Studies are currently focused on discovering cerebral metabolic processes underlying sleep and motor behavior.

The LABORATORY OF BRAIN EVOLUTION AND BEHAVIOR (Paul D. MacLean, M.D., Chief; Senior Staff: John B. Calhoun, Ph.D., and Walter C. Stanley, Ph.D.) offers opportunities for research on evolutionary, developmental, and ecological factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals, living under seminatural conditions. The laboratories are equipped for neuroanatomical research, microelectrode recording, brain stimulation, and psychological testing and automated monitoring of behavior. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior. Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, etiology, psychology, and ecology. The laboratory is beautifully located at the NIH Animal Center near Poolesville, Maryland, with open fields, a large pond for water fowl, and woodlands.

The DIVISION OF SPECIAL MENTAL HEALTH RESEARCH (F. E. Bloom, M.D., Acting Director) located at Saint Elizabeths Hospital, (1) plans and conducts a program of intramural research on special mental health problems such as psychopharmacology, neuropharmacology, memory, and human behavior and (2) performs clinical evaluation and followup activities in connection with research patients.

The LABORATORY OF CLINICAL PSYCHOPHARMACOLOGY (Richard J. Wyatt, M.D., Acting Chief; Senior Staff: Dr. J. C. Gillin, Dr. T. Reynolds, Dr. Lewellyn Bigelow, Dr. F. Karoum, and Dr. R. Stillman) uses biological techniques to study both specific and generalized systems operating in the normal human brain. Chemical, physiological, and psychological behavior of these normal systems is compared to putative abnormal ones in psychiatric patients. The comparisons of normal and abnormal behaviors lead to hypotheses as to cause and possible treatment. The principle behavioral abnormality studied is schizophrenia although presenile dementia, aging, and problems of drug abuse are also investigated. The laboratory operates three research wards consisting of about 12 beds each in which a variety of pharmacological, physiological, sleep, biochemical, and psychological studies are conducted on psychiatric patients and normal volunteers. The laboratory is equipped with physiological and chemical equipment including gas chromatography, mass spectrometry, as well as computer and animal facilities. Because of the diversity of approaches used, the laboratory seeks applicants who have both clinical and laboratory interests.

The Laboratory of Neuropharmacology (F. E. Bloom, M.D., Chief; Senior Staff: Dr. B. J. Hoffer, Dr. G. R. Siggins, Dr. F. F. Weight) conducts a multidisciplinary research program centered upon the identification of synaptic transmitter substances, and the mechanisms by which neuro-active and psycho-active drugs exhibit effects upon synaptic transmission. The approach is entirely at the cellular level, utilizing intracellular and extracellular electrophysiologic techniques, micromethods of drug administration including microelectrophoresis, and cytochemical studies with light, fluorescence, and electron microscopy. Specifically, studies are currently being carried out on: (1) the characterization and pharmacology of potential monoamine-containing neuronal pathways in the mammalian central nervous system; (2) the relation between pharmacological responsiveness and development of structurally specialized synapses; and (3) the cytologic and physiologic organization of sympathetic ganglia.

The Laboratory of Preclinical Pharmacology (E. Costa, M.D., Chief) conducts research in neurochemistry and neuropharmacology to elucidate control mechanisms involved in the clinical response of drugs affecting neuronal function. The laboratory is organized into three sections: (1) The Section on Molecular Pharmacodynamics (E. Costa, M.D., Chief; Senior Staff: D. L. Cheney, Ph.D., D. M. Chuang, Ph.D., H. LeFevre, Ph.D., J. Meek, Ph.D., and P. Uzunov, M.D., Ph.D.) conducts pharmacological studies on: (a) the dynamics of catecholamine and indolealkylamines in discrete brain nuclei using pulse labeling with 18_{02} and mass fragmentography to measure turnover rate of these putative neurotransmitters; (b) the dynamics of acetylcholine in discrete brain nuclei using pulse labeling with deuterated precursors and mass fragmentography to measure turnover rate of acetylcholine; (c) the regulation of the biosynthesis of the rate limiting enzymes that control the turnover of neurotransmitters; and (d) the regulation of cyclic nucleotide phosphodiesterase activity by endogenous proteic activators. (2) The Section on Biochemical Pharmacology (N. H. Neff, Ph.D., Chief; Senior Staff: H-Y. Yang, Ph.D.) conducts investigations directed at: (a) measuring turnover rates of regulatory enzymes of the dynamics of putative brain neurotransmitters; and (b) identifying and characterizing enzymes controlling the metabolism of endogenous polypeptides in the brain. (3) The SECTION ON NEUROENDOCRINOLOGY (A. Guidotti, M.D., Chief) conducts studies concerning (a) the molecular mechanisms involved in the trans-synaptic induction of tyrosine hydroxylase; (b) the activation of cAMP dependent protein kinases in relation to the neuroendocrine control of pituitary and pineal glands; and (c) the role of cGMP and cAMP in the synaptic action of amino acids functioning as neurotransmitters.

National Institute of Neurological and Communicative Disorders and Stroke

Donald B. Tower, M.D., Ph.D., Director

General. The National Institute of Neurological Diseases and Stroke conducts, fosters, and coordinates research on the causes, prevention, diagnosis, and treatment of neurological and sensory disorders and related fields, and administers a program of research and training grants and awards.

Throughout the Institute, opportunities also exist for clinical and professional education, including many scientific disciplines.

Intramural Research Program

Thomas N. Chase, M.D., Director

Donald B. Calne, M.D., Clinical Director

The Medical Neurology Branch (W. King Engel, M.D., Chief) has as its major function the application of basic research techniques to the investigation of clinical neurological problems. The Clinical Associate becomes acquainted with a majority of the neurological diseases with particular emphasis on the disorders of muscle, myasthenia gravis, lower motor neuron diseases, metabolic abnormalities of the central nervous system, and genetically determined disorders. He receives instruction in clinical neurology and the related clinical and basic sciences while developing an understanding of the various laboratory techniques which support the neurological investigation. During the first 12 months he is in a ward environment and is responsible for the care of patients on the Medical Neurology Service and the integration of related research. He covers the neurologic consultations to the other clinical services during 3 of those months. During the first year he is expected to learn to perform one of a variety of basic laboratory techniques (such as histochemistry, tissue culture, biochemistry, electron microscopy, immunology, autoradiography, or electromyography) as it applies to a clinical problem. The second year is spent in full-time work on that clinical research technique. Some Clinical Associates may stay a third year to continue their clinical research activities. The program is accredited for 1 year of residency training in neurology.

The Surgical Neurology Branch (Ayub K. Ommaya, M.D., F.R.C.S., Acting Chief) investigates problems in neural trauma, brain tumors, the surgical prophylaxis of strokes, and cerebrovascular disease management.

The Clinical Associate is required to study and has responsibility for the care of patients with brain tumors, strokes, and vascular malformations of the nervous system, and others with a variety of neurological disease. He receives practice and instruction in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating theater. He is also assigned to one of a number of laboratory projects designed to provide animal model correlation with the human disease under study. He is expected to learn and use new experimental techniques and work in collaboration with Senior Scientists.

The BRANCH OF CLINICAL NEUROSCIENCES (Cosimo Ajmone Marsan, M.D., Chief) consists of two sections: Clinical Neurophysiology and Functional Neurosurgery. The Branch involves a relatively small, highly specialized patient population in addition to that referred from the entire Clinical Center for EEG examination. The position of Clinical Associate in Neurosurgery is for a 2- or 3-year appointment. Preference is given to persons with basic neurological or neurosurgical training. Appointments in neurophysiology are also for 2 or 3 years. Preference is given to people with some previous experience in the field of electrophysiology and a knowledge of neuroanatomy. Current research: Experimental epilepsy, involuntary movements, thalamo-cortical relationship, nature of brain waves, microelectrode study of cortical neurons, etc.

The DEVELOPMENTAL AND METABOLIC NEUROLOGY BRANCH (Roscoe O. Brady, M.D., Chief; Anatole S. Dekaban, M.D., Associate Chief for Clinical Investigation). The branch is devoted to cross-disciplinary basic investigations and clinical studies of disorders of the nervous system. The research deals with (1) the pathological biochemistry, diagnosis, and therapy of inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, and Tay-Sachs disease; (2) functional abnormalities of the nervous system, including epilepsy; (3) heritable and acquired demyelinating conditions such as multiple sclerosis; and (4) the metabolism of complex lipids in tumorigenic virus-transformed cells.

The branch is comprised of the Section on Enzymology and Genetics (Dr. R. O. Brady, Head), the Section on Neurochemical Methodology (Dr. A. E. Gal, Head), and the Section on Clinical Investigations and Therapeutics (Dr. A. S. Dekaban, Head). The first two sections are primarily devoted to basic research; in- and outpatient study is included in the Section on Neurological Development.

The INFECTIOUS DISEASES BRANCH (J. L. Sever, M.D., Ph.D., Chief) conducts clinical and laboratory investigations of infections which damage the developing fetus and the human central nervous system. The branch is divided into three sections: (1) Immunochemistry and Clinical Investigations, (2) Neurovirology and Bacteriology, and (3) Experimental Pathology. These sections utilize immunological techniques for cellular and humoral immune responses, human volunteer and clinical trials, virology, microscopy, as well as experimental pathology with small animals and nonhuman primates. Current emphasis is on perinatal infections which damage the developing fetus; the detection of acute infections of the central nervous system; chronic central nervous system viral infections such as subacute sclerosing panencephalitis, and vaccine development for viruses which affect the central nervous system.

LABORATORY OF NEUROPHARMACOLOGY (Thomas N. Chase, M.D., Chief) conducts basic as well as clinically applied studies of central neurohumoral mechanisms and their relation to the pathogenesis of various disorders of nervous system function. Current research projects include (1) preclinical studies of the synthesis, metabolism, release, and receptor interactions of monoamines, δ-aminobutyric acid and other central neurotransmitters; (2) mechanisms of action of drugs which affect the nervous system; (3) clinical and biochemical studies of patients with disorders such as parkinsonism, epilepsy, and amyotrophic lateral sclerosis; and (4) clinical assessment of new therapeutic agents.

LABORATORY OF NEURO-OTOLARYNGOLOGY (Jorgen Fex, M.D., Ph.D., Chief). This laboratory is a new facility. The mammalian inner ear is being studied, using techniques of anatomy, biochemistry, and neurophysiology. A project is underway to study inner ear mechanisms of synaptic excitation in the mammal. A major, long-term program of the laboratory is to solve problems concerning hereditary hearing disorders in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models. It is expected that experiments on cultures of the mouse hearing organ will be initiated.

LABORATORY OF NEUROCHEMISTRY (R. Wayne Albers, Ph.D., Acting Chief) directs research toward the elucidation of chemical attributes of neural tissues which underlie the normal functioning of the nervous system and the derangements of function in various neurological diseases. The investigations, which are primarily at the basic level, are distributed among three sections of the laboratory: The Enzyme Chemistry Section (Head, Dr. R. W. Albers), Section on Neuronal Development and Regeneration (Acting Head, Dr. A. A. Zalewski), and the Physiology and Metabolism Section (Head, Dr. E. G. Trams). In these investigations a wide variety of disciplinary approaches and methodologies, including tissue culture and appropriate clinical material, are being utilized. Special emphasis is given to the relevance of the various laboratory programs to neurophysiological problems, such as mechanisms subserving reception, conduction, and transmission of nerve impulses, and to clinical problems, such as the bases for epilepsy, cerebral edema, stroke, tumors, demyelinating diseases, and nutritional and genetically-determined disorders.

The LABORATORY OF MOLECULAR BIOLOGY (Ernst Freese, Ph.D., Chief) examines the molecular mechanisms of biological processes that are affected in hereditary and viral diseases or in teratogenic effects.

In the SECTION ON REGULATION OF NUCLEIC ACID SYNTHESIS (Dr. R. A. Lazzarini, Head) the control of cellular and viral RNA synthesis is studied in tissue cultures. In particular, the transcription and replication of the myxo- and paramyxo-viruses is examined at the molecular level.

In the SECTION ON DEVELOPMENTAL BIOLOGY (Dr. Ernst Freese, Head) the transport of substrates through cellular membranes and other membrane-associated phenomena are studied in growing and differentiating bacteria and tissue cultures, as well as in isolated membrane vesicles. The inhibition of these reactions by lipophilic compounds, present in the human environment and partly known to have neurological effects, is analyzed. In addition, the section determines the biochemical reason why compounds accumulating in cacogenic mutants prevent normal development or produce hereditary diseases, and it endeavors to find means of avoiding this accumulation or preventing its effect. Bacterial systems, with their powerful genetic and biochemical possibilities, are compared with human tissue cultures.

The LABORATORY OF NEUROPATHOLOGY AND NEUROANATOMICAL SCIENCES (Igor Klatzo, M.D., Chief) recognizes scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomical sciences. Thus investigations on basic pathogenic mechanisms operative in various neuropathological conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system. Specific problems under current investigation are: Cerebral ischemia, hypoxia, brain edema, role of the glia, development and pathology of myelin, control of carbohydrate metabolism, aspects of vascular permeability and transport mechanisms in the brain, mechanisms of neurohormonal regulation, localization of catecholamines, elucidation of some of the sensory and motor systems, investigation of neural membranes, junctional complexes, as well as the source and fate of synaptic vesicles. The main technical approaches include light and electron microscopy, freeze-fracturing, histochemistry, radioisotopic, biochemical and microchemical assays, and tissue culture. The laboratory is divided into seven sections:

(1) the Section on Functional Neuroanatomy (Thomas Reese, M.D., Head),

(2) the Section on Neurocytology (Milton Brightman, Ph.D., Head),

(3) the Section on Experimental Neuropathology, (Jan Cammermeyer, M.D., Head),

(4) the Section on Cerebral Vascular Pathology (Igor Klatzo, M.D., Head),

(5) the Section of Cellular Neuropathology (Henry Webster, M.D., Head),

(6) the Section on Cellular Neurochemistry (Janet Passonneau, Ph.D., Head), and

(7) the Section of Neurocytobiology (Maria Spatz, M.D., Head).

The LABORATORY OF NEUROPHYSIOLOGY (M. G. F. Fuortes, M.D., Chief) conducts research on basic properties of nerve cells and on the organization of the nervous system. The *morphology* of cells, synapses and subcellular structures is studied by means of optical and electron microscopy. *Membrane properties* of receptor cells and central neurons are investigated by electrophysiological methods. Work on *receptor functions* include kinetic studies aimed at determining the properties of the transduction processes. The properties of *central neurons and synapses* are studied in simple preparations derived from vertebrates and invertebrates. Electrical and chemical properties of cells in *tissue culture* are also being investigated.

The LABORATORY OF EXPERIMENTAL NEUROLOGY (William F. Caveness, M.D., Chief) includes the following activities: (1) the investigation of the delayed effects of high energy radiation to the whole brain of the Macaca mulatta according to clinical therapeutic regimens. The functional alterations are monitored with clinical examinations, funduscopic photography, and chemical analyses of CSF fluid at four week intervals following exposure. At eight week intervals, the brains are subjected to the definitive histological examination at a collaborating facility, (2) the study of development and propagation of focal seizures in the developing brain of the monkey with the use of electrophysiological and regional blood flow techniques. Particular attention is directed to the subcortical nuclear masses.

One Research Associate position is available for 2 to 3 years. Previous experience in electrophysiology or neuroanatomy is essential.

The LABORATORY OF NEURAL CONTROL (Robert E. Burke, M.D., Acting Chief) conducts fundamental research on the properties of mammalian nerve cells and on the organization of the mammalian central nervous system with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1.) the central nervous system control of spinal cord motoneurons and the control exerted by these cells in turn on the muscle fibers innervated by them; 2.) the organization of information processing systems in the spinal cord; and 3.) the activity of central neurons and peripheral afferents during normal movement in intact animals. Such studies utilize both established and newly developed techniques for electrophysiological recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The Laboratory has facilities for development of specialized experimental equipment and novel electrode designs, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

The CENTRAL NERVOUS SYSTEM STUDIES LABORATORY (D. Carleton Gajdusek, M.D., Chief) is engaged in two studies: (1) child growth, development, behavior, and learning in primitive cultures, and (2) slow, latent, and temperate virus infections of the central nervous system. Much of the program derives from the study of the disease kuru and Creutzfeldt-Jakob disease, and similar subacute degenerative disorders which have been successfully transmitted to the chimpanzee and other nonhuman primates and cultivated *in vitro* in tissue cultures of brain cells. The biological and molecular characterization of the atypical viruses causing these diseases is a major focus of this work. The child studies involve all aspects of the cultural and physical anthropology of native people in relation to their environment, as well as repeated medical, genetic, and microbiological examination of these intensely studied groups. Research films are prepared on many aspects of learning and socialization in these primitive peoples and investigative uses of cinema are developed.

Neurological Disorders Program

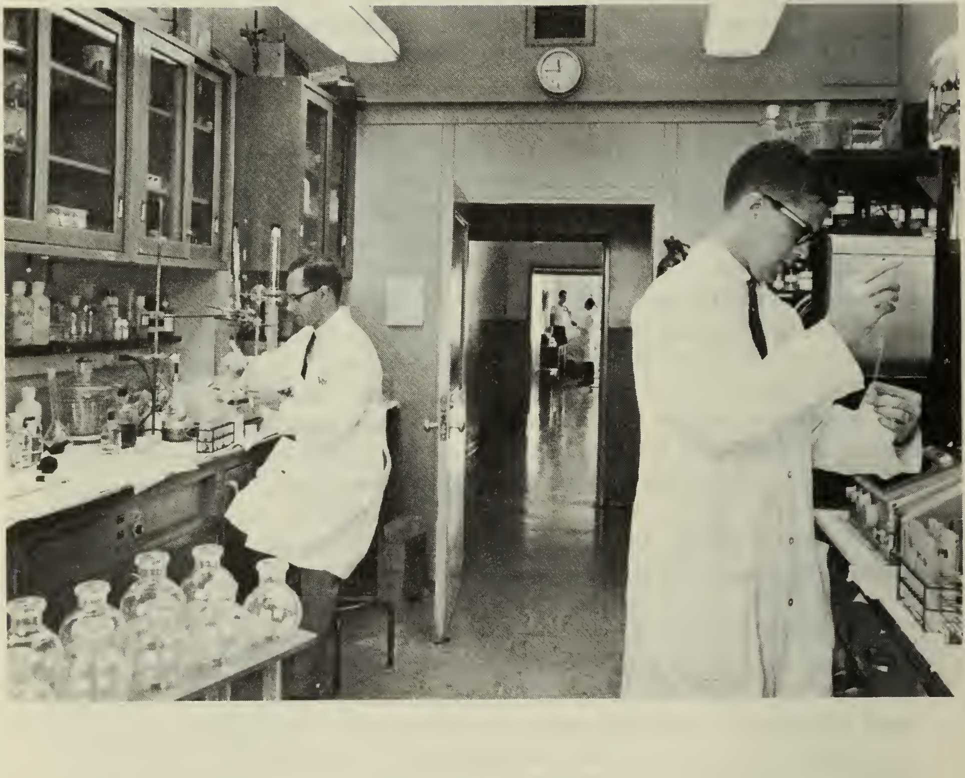
J. Kiffin Penry, M.D., Director

The goal of the Neurological Disorders Program is to plan and direct a program of grant and contract support for research and research training on neurological disorders to insure maximum utilization of available resources in attainment of Institute objectives; and to collaborate with intramural programs in the Institute and NIH-wide. The program is charged with the study of national priority diseases such as epilepsy, developmental disorders of children and adults, sclerosing and neuromuscular disorders, infectious diseases and tumors of the central nervous system, neuroendocrine studies, and learning, behavior and other sensory disorders. A number of the studies underway are collaborative studies which encompass the input of a number of outside institutions. The following programs are conducted by the Neurological Disorders Program of NINCDS.

The EPILEPSY BRANCH, under J. Kiffin Penry, M.D., develops and coordinates organized and directed research programs on a multi-institutional geographic, or multidisciplinary basis; develops, conducts, and coordinates collaborative and directed research programs aimed at finding new methods of diagnosis, treatment, and prevention of convulsive disorders; synthesizes, screens, studies the pharmacology, and clinically evaluates antiepileptic drugs within its own facilities or supports these activities through extramural contracts or grants.

The DEVELOPMENTAL NEUROLOGY BRANCH, under Joseph S. Drage, M.D., plans and implements a program of grant and contract supported research on the neurological basis of developmental disorders of children, including the areas of cerebral palsy, autism, mental retardation, learning and behavioral disorders, central nervous system birth defects, heritable muscle and neurological diseases, and minimal brain dysfunction; assesses need for research and research training in such areas; determines and recommends program priorities and funding levels for such areas; consults with professional and voluntary health organizations in identifying, developing, and implementing a research program focused on the neurological basis of developmental disorders of children; provides for the archival and retrieval system of the Collaborative Perinatal Project data and promotes the appropriate use of this national data resource commensurate with the goals and mission of the NINCDS.

The NEUROIMMUNOLOGY BRANCH (Dale E. McFarlin, M.D., Chief) has recently been established. This group is doing research in the following area: (1) Characterization of the immune response to viral agents; in particular agents such as measles which cause chronic infection in patients with neurological diseases, and certain animal models are being studied. (2) Assessment of the immune response to membrane components of membranes in the peripheral and central nervous system. (3) Evaluation of immune function in patients with chronic neurological disorders of unknown etiology such as multiple sclerosis and parkinsonism which may be related to either an atypical infection of the nervous system or immunopathologic mechanisms. (4) Projects involving the clinical assessment of new therapeutic agents are planned in the future.



The Clinical Center

Roger L. Black, M.D., Acting Director

Roger L. Black, M.D., Associate Director

Philippe V. Cardon, M.D., Associate Director

The Clinical Center appoints Clinical Associates for the Departments of Diagnostic Radiology, Blood Bank, Clinical Pathology, and Nuclear Medicine. Associates in Diagnostic Radiology are expected to have completed their residencies prior to entrance on duty.

The BLOOD BANK DEPARTMENT (Paul V. Holland, M.D., Chief) is accepting applications for Clinical Associates under the matching system. Applicants with at least 1 year of training post internship are preferred.

The Department supplies over 20,000 blood products annually for transfusion to patients with unique hematologic and immunologic problems. The use of blood components is stressed, with increasing emphasis on the use of frozen red cells in appropriate clinical situations. The medical staff consists of four full-time staff physicians and one clinical associate, as well as residents and medical students who are present for varying periods of training.

In addition to its service function, a significant proportion of Blood Bank activity is oriented toward clinical and basic research. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various Institutes. Current programs include investigations into hepatitis and the hepatitis B (Australia) antigen, the effects of biologic imcompatibilities on transfusion and transplantation, immunologic studies of drug-induced hemolytic anemias, and the use of computers in laboratory medicine.

The program offers training for the clinician in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. A close professional liaison is maintained with the Clinical Pathology Department through an active program of lectures, rounds, and seminars.

The CLINICAL PATHOLOGY DEPARTMENT (Ronald J. Elin, M.D., Ph.D., Chief) is accepting applications for Clinical Associates whose interests lie in specialized training and research in laboratory medicine. The department is organized into four main services: Clinical Chemistry, Hematology, Microbiology, and the Laboratory Computer Service. These areas are staffed by over 100 professional and technical personnel who form the operational base for the broad spectrum of laboratory diagnostic services called upon by the various Institutes for their intramural patient care programs. In addition, the professional staff of the department is engaged in collaborative and independent research in the areas relevant to laboratory medicine and the clinical diagnostic problems encountered at the Clinical Center. The department participates in the training of Residents in Clinical Pathology and interacts fully and on a professional consultative basis with the clinical programs at the National Institutes of Health.

Among the procedures and programs currently in operation in the department are automated assay systems for laboratory diagnosis, carbohydrate chromotography, amino-acid analysis, gas chromatography, radioimmunoassays, mineral metabolism studies, coagulation factor studies, certain host-defense mechanisms in infectious diseases, properties of bacterial endotoxins, diagnostic anaerobic bacteriology, and new approaches in the interface between computer assisted laboratory automation and data processing. These latter programs, in particular, are facilitated by direct access to the department's own computer facilities.

A close professional liaison is maintained with the Blood Bank Department.

A Clinical Associateship in any of the four services offers a broad experience in clinical and laboratory medicine. Each service carries on an active consultative role and participates extensively with many of the clinical services. In addition, each service provides supervised instruction in the functions of that area and opportunities are available for developmental investigation of the procedures of the clinical laboratory.

The DEPARTMENT OF DIAGNOSTIC RADIOLOGY (John L. Doppman, M.D., Chief).

Four Clinical Associates are selected each year from among those applicants who have completed their residencies in Radiology or Diagnostic Roentgenology (Board certification not required). Such appointments are made for a period of 2 years with occasional opportunity for reappointment.

The department is well equipped to provide the usual routine and special diagnostic radiographic examinations needed by the 27,500 patients seen each year. The preselection of patients for admission to the NIH insures a challenging and stimulating gamut of diagnostic problems.

Twelve radiologists comprise the professional staff and an adequate supporting staff is provided.

Facilities are available for both collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

The DEPARTMENT OF NUCLEAR MEDICINE (Gerald S. Johnston, M.D., Chief). One Clinical Associate is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in Nuclear Medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved Internal Medicine, Radiology, or Clinical Pathology is recommended in order to meet the requirements for certification by the American Board of Nuclear Medicine.

The American Medical Association has approved the department for a 2-year residency training program in Nuclear Medicine. Qualifications for trainees include at least 2 years of prior training in Radiology, Pathology, or Internal Medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital and the Washington Hospital Center.

The department consists of four sections: Diagnostic Nuclear Medicine Section, Whole Body Counter Section, Radiopharmacy Section, and Applied Physics Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various Institutes working within the Clinical Center. Dual probe rectilinear scanners and gamma cameras are the basic imaging devices. Dedicated computers supported by NIH computer experts from DCRT are located within the section. The Applied Physics Section and DCRT personnel work cooperatively in the development of new diagnostic techniques. The Whole Body Counter Section works closely with the Diagnostic Section and the Radiation Safety Office. It operates three whole body counters and provides a consultation service to all the Institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staff of the Diagnostic and Whole Body Counter Sections consists of seven physicians, a radiobiologist, a nuclear physicist, an equipment specialist, seven nuclear medical technicians, and three clerks. Departmental professionals are encouraged to interact with members of the various Institutes in order to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases.

The Radiopharmacy Section employs three full-time radiopharmacists, a technician, and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by Diagnostic Nuclear Medicine. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

PART FOUR

Academic Programs Available to Associates

Among the academic programs open to an NIH Associate are: Evening courses provided by the Foundation for Advanced Education in the Sciences, Inc.; formal seminars under the direction of NIH staff; Combined Clinical Staff Conferences; formal lectures; symposia; and an annual scientific equipment exhibit. The "N.I.H. Calendar of Events" lists 25 to 30 programs each week. Other events of interest are held at universities and other institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. Established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science, the Foundation is a non-Federal independent organization as defined by the Government Employees Training Act; however, its tuition and other fees can be paid by a Federal employer. Courses are offered in two semesters, fall and spring; courses are offered at the undergraduate and graduate levels under the programs of its several departments of instruction: Behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages and general studies. Further inquiries regarding The Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, Md. 20014.

Seminars

An NIH Program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators, and gives them the additional opportunity to master selected topics not adequately covered during college or graduate schooling. These exercises are an integral part of the Associate Program and are geared specifically in that direction. The program accommodates Research, Staff, and Clinical Associates and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics; mathematics and physical chemistry; cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of a qualified expert in the field. In preparation for these, the Associate does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate Institutes engaged in clinical research, the Clinical Center sponsors at least one monthly Combined Clinical Staff Conference for 9 months of the year. Each conference is conducted by one of the Institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff, and serve to keep individual investigators abreast of current emphasis in all clinical research.

Several formal lectures are presented annually. The National Institutes of Health Lecture Series was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the Scientific Directors of the Institutes. The R. E. Dyer Lectureship was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942–50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science; and is administered by NIH.

The Jules Freund lecture series was established in 1961 and is presented annually in honor of the first Chief of the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases.

The G. Burroughs Mider Lectureship was established in 1968 by the Scientific Directors to honor Dr. Mider for his distinguished service to NIH. On advice of the Scientific Directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Equipment Exhibit: Symposia

The NIH Research Equipment Exhibit was established in 1951 to acquaint scientists with the most modern research tools and to give them an opportunity to discuss equipment problems with representatives of industry. In 1954, a Symposium on Recent Developments in Research Methods and Instrumentation was added, offering a balanced presentation by specialists in many areas of biomedical research. The two annual events combined to provide a convenient setting for the exchange of information between research investigators and manufacturers of scientific equipment.

The NIH International Symposium on Biomedical Research was established in 1963 to emphasize the mutuality of interest of NIH and the international scientific community, particularly with the extension of NIH programs overseas.

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Naval Medical Center, offer exceptional opportunities. Some Associates find the time to pursue a certain amount of formal education at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located in the Clinical Center) provides a central facility for the scientific, medical, administrative and supportive staff engaged in the NIH research program. As a self-service, open-stack library, it contains a collection of 110,000 volumes and receives annually 5,000 monographs and 3,000 foreign and domestic journals. In addition to the usual library services, the NIH Library provides on-line access to NLM's medical literature data banks, advisory services for literature needs, and a translating service.

The National Library of Medicine is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 1 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service National Institutes of Health

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ASSOCIATE TRAINING PROGRAMS IN THE Medical and Biological Sciences at the National Institutes of Health

1977 CATALOG

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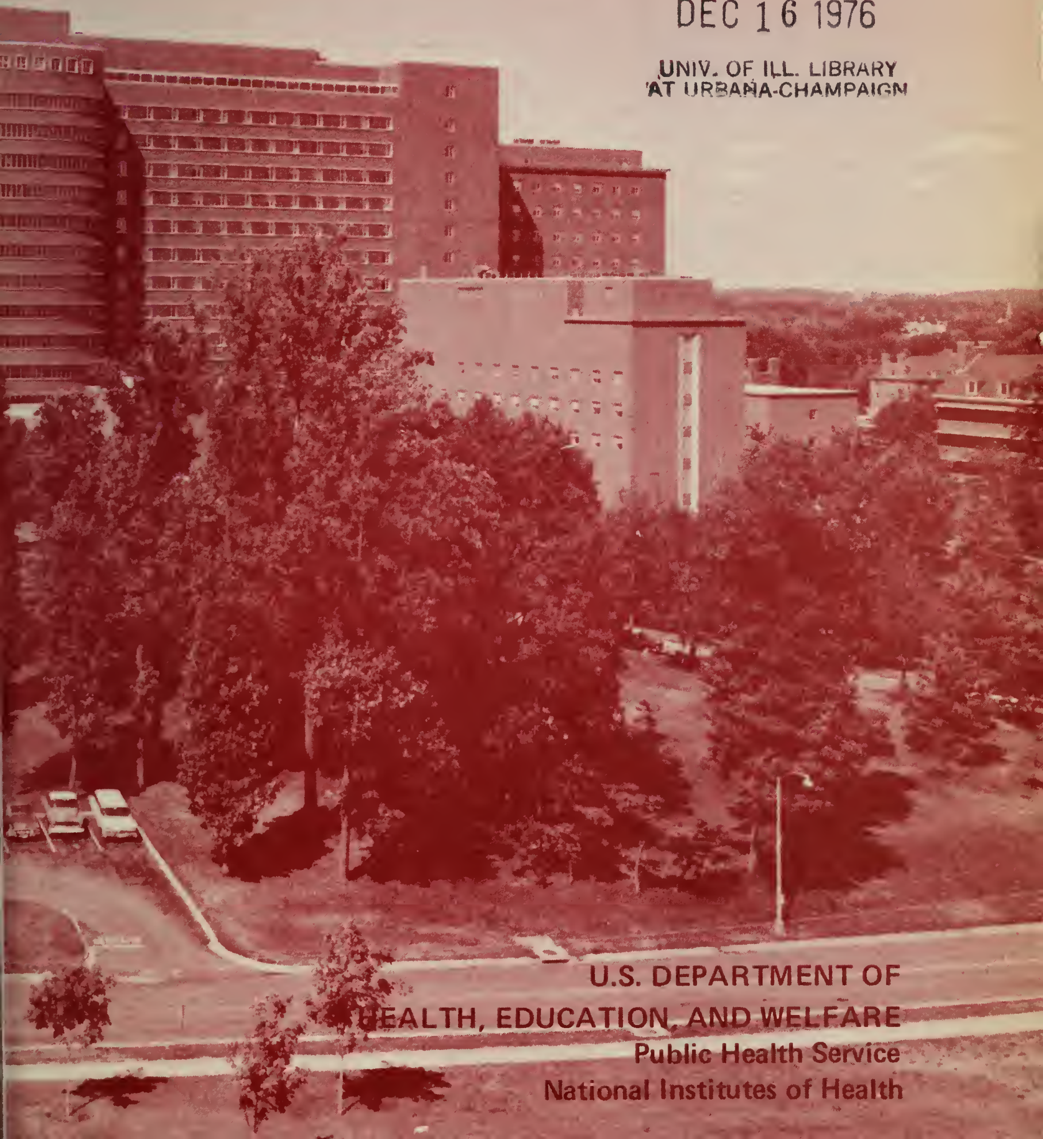

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

February 15	Deadline for receipt of completed NIH Associate applications

FOREWORD

The National Institutes of Health is the primary biomedical research arm of the Federal Government and is dedicated to the broad missions of improving health and curing disease. To do this, it supports biomedical research and training throughout the country and conducts its own research programs.

The NIH intramural research facilities are located on a 306-acre campus in Bethesda, Maryland. The Clinical Center, the hospital for clinical investigations, has 541 beds and more than 1,000 laboratories. The 4,500 patients admitted during the past year participated in many of the 1,400 research projects. The professional staff at NIH comprises 2,000 investigators with doctoral degrees, over half of whom are physicians.

The association with scientists and physicians of international repute fosters the spirit of scientific inquiry and medical research. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Associate Program at the NIH.

Mortimer B. Lipsett, M.D.
Director
The Clinical Center

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PART ONE

General Description of Associateships and Other Opportunities

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OPPORTUNITIES for training and experience in clinical and laboratory investigation are available to physicians and dentists who receive appointments as Clinical, Research, and Staff Associates at the National Institutes of Health. These positions encompass most of the medical specialties as well as the basic science disciplines.

Appointments to the Associate Training Program are based on intellectual attainment and demonstrated research interest and ability. An individual's background in research is often decisive in making selections but sometimes clinical expertise in a specialty is the main criterion. Selections are made through a matching process, explained in Part Two.

Each Associate participates in a research program under the direction of a preceptor. Preceptors help Associates to enrich their experience in research and in other ways. The research responsibilities and latitude given to Associates depend on their capacities, interests, and initiative.

Teaching sessions designed to complement Associateships are held regularly. In addition, postgraduate instruction is available through evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. (See Part Four). Associates in many program areas are expected to take advantage of academic opportunities on the NIH campus.

A candidate may enter the Associate Program as a member of the Public Health Service Commissioned Corps, or as a nontenured civilian employee.

All applicants are carefully considered. NIH welcomes applications from women and members of all minority groups.

The Clinical Associate

The Clinical Associate participates in both clinical and laboratory research. Institute programs differ in the proportion of time devoted to laboratory and clinical responsibilities.

Clinical activities are under the immediate supervision of senior investigators, and include rounds, conferences, and other instructive exercises. The proximity between the patients and collaborating scientists from many biological disciplines has created an unusual environment for clinical investigation. The environment is also enriched by the presence of medical students from all parts of the country with whom Clinical Associates have close contact and share responsibility for patient care.

Clinical Associates are not in formal residency training programs, even though they may be performing many of the same functions that residents do in other hospitals. Some Associates appointed to Dermatology, Neurology, Psychiatry, and Nuclear Medicine programs are recommended for a limited amount of residency credit by their respective program chiefs. Associates in positions that provide further training in Internal Medicine have often received credit toward their required 3 years of training upon application to the American Board of Internal Medicine—the so-called "short track." However, the Board intends to phase out the short track option. It is doubtful that clinical training completed later than June 1979 will be considered for credit.

The Dental Clinical Associate

Like his physician Clinical Associate counterpart, the Dental Clinical Associate may participate in laboratory and clinical research, and at the same time enhance his professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the Associateship, full opportunity is provided for: (1) familiarity with all ongoing research programs relevant to dentistry; (2) affiliation with one or more preceptors for participation in a mutually acceptable area of investigation; and (3) extension of scientific background through rounds, conferences, seminars, and formalized course work.

The Research Associate

The Research Associate devotes most of his time to laboratory research in a biomedical science. His preceptor is responsible for training him in research methodology and design, and for guiding him in the conduct of specific research undertakings and in the interpretation of results. A goal is to select research problems which will enable the Associate to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The Pharmacology Research Associate

Sponsored by the National Institute of General Medical Sciences, Pharmacology Research Associates spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those who have made a commitment to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

The Staff Associate

The Staff Associate position provides opportunities for those highly qualified candidates who could contribute significantly to research in areas which are not specifically designated in the Research or Clinical Associate categories. The Staff Associate may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he works. Research experience may be supplemented by formal evening study courses, as well as by attendance at lectures by guest speakers and a variety of regularly scheduled seminars.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to students from any of the nation's medical schools. For 1977–78, the staffs of several Institutes are collaborating to supply an in-depth exposure to ten clinical subspecialties: Computers in Clinical Medicine, Endocrinology and Metabolism, Gastroenterology, Genetics, Immunology, Infectious Diseases, Nuclear Medicine, Oncology-Hematology, Psychopharmacology, and Surgical Oncology.

The essence of this educational experience is a close association between the student, clinical associates, and physician-scientists in several of the Institutes.

Students have patients assigned to them for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with particular interests in fields other than those listed above are sometimes arranged through communications between an NIH staff member and a faculty sponsor of the student.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Associate Director for Medical Education
The Clinical Center
National Institutes of Health
Bethesda, Md. 20014

Residency Programs

Fully approved residency programs are offered in anatomical pathology, clinical pathology, and combined clinical and anatomical pathology.

In 1974 the American Medical Association established requirements for a residency in blood banking; it is expected that an approved blood bank residency program will be functioning in 1977.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Ronald J. Elin, M.D., Ph.D.
Chief, Clinical Pathology Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

Louis B. Thomas, M.D.
Chief, Laboratory of Pathology
National Cancer Institute
National Institutes of Health
Bethesda, Md. 20014

Paul V. Holland, M.D.
Chief, Blood Bank Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

On the basis of agreements between program chiefs and appropriate American Specialty Boards, Clinical Associates in dermatology, psychiatry, and neurology may receive credit for 1 year each, and 2 years in nuclear medicine.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as Associates, but as Staff Physicians. Initial appointments are temporary and usually for 2 years, but some Staff Physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part time in ongoing research.

PART TWO

Applying for an Associateship

About 100 Clinical Associates and 50 Research and Staff Associates are appointed annually. Associates may be employed through the Commissioned Corps of the Public Health Service or through a Civil Service mechanism. Of course, if applying through Civil Service, it is not necessary to submit the PHS commissioning forms.

Applicants usually apply during their third or fourth year of medical school for entrance on duty two years later. However, some Associate positions are appropriate for persons currently in their intern or residency training. The applicant should designate on his application the year or years he wishes his associateship to begin. Most appointments will be for 1979, and a few will be available for 1978.

To be considered for a Clinical, Research, or Staff Associate appointment, the following forms must be received in the NIH Associate Office, National Institutes of Health, Bethesda, Md. 20014:

- Information Record for Clinical, Research, and Staff Associate Positions
- Program Area Selection Check List
- NIH Associate Information and Status Record
- Interview Information Record
- Application for Appointment as a Commissioned Officer in the Public Health Service (2 copies)
- Fingerprint Chart (fingerprints may be obtained at PHS facilities, local police, or post office)
- Data for Nonsensitive or Noncritical Position.

The applicant is responsible for requesting the following materials to complete the application:

- Three sets of references from professional persons whom the candidate has listed on the NIH information sheet. Each set consists of: (1) Request for Confidential Evaluation of Applicant for Appointment as an NIH Associate; and (2) Reference Request (Commissioned Corps)
- Two copies of all college and medical or dental school transcripts (showing class standing, if available).

Public Health Service Commissioned Corps

The Commissioned Corps is a uniformed service similar in many respects to the Army, Navy, and Air Force. It is a uniquely "all officer"

Corps, comprised largely of professionals in medical and health related fields.

Pay, allowances, and other benefits are comparable to those of officers of the Armed Forces. Benefits include medical care for officers and dependents; tax-free allowances for quarters and subsistence; commissary, post exchange, and officers' club privileges; and 30 days annual leave.

While most career PHS officers are eligible for the variable incentive pay (VIP) "bonus," VIP is not an immediate incentive to prospective Associates. Officers serving in their first 2 years as Associates, and officers performing obligated service incurred through participation in Senior COSTEP Program are *not* eligible for VIP.

For those considering longer periods of service or careers in the PHS, the advantages of subsequent VIP, and of noncontributory retirement and survivor benefit plans are substantial.

To be eligible for the Commissioned Corps for participation as an NIH Associate, a candidate must meet the following requirements:

1. Be a United States citizen.
2. Meet the medical fitness standards.
3. Be a graduate of an accredited medical or dental school.
4. Satisfactorily complete an internship approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)

Civilian Staff Fellowships

As an alternative to the Commissioned Corps, Associates may be appointed as Staff Fellows. This is a temporary Civil Service appointment. Salaries are similar to those of Commissioned Corps officers who do not receive the variable incentive pay "bonus." Medical fitness standards are less stringent, and noncitizens of the United States who are eligible for naturalization within 4 years may be appointed. Usually, Fellows earn slightly less annual leave. Comparative advantages of retirement plans and fringe benefits depend largely on individual circumstances and preferences.

Early Commissioning Program for Medical Students (PHS Senior COSTEP Program)

Qualified candidates who will be in their senior or last year of medical school during academic year 1977–78 may apply for an Associateship through this program. Candidates may apply for duty to begin either (1) following one or more years of residency training or (2) immediately after internship.

Successful candidates are appointed and placed on active duty as commissioned officers in the Reserve Corps of the Public Health Service during their senior or final year. They receive full pay and allowances as Junior Assistant Health Service Officers (equivalent to Navy Ensign), plus payment of tuition, fees, and other related expenses. In return for this financial support, they are obligated to serve on active duty as medical officers with the PHS for a minimum of 2 years.

Applications cannot be considered from members of another uniformed service or anyone having a service commitment upon graduation other than to the Public Health Service.

Method of Selection—Matching Program

Selections for the Clinical, Research, and Staff Associate appointments are made through a matching process in which the candidate's preferences are matched with the Institute preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Check List." After reading Part Three of this catalog, he should check off on these sheets the areas in which he is interested. He does not indicate his preferences at this point, and he is not limited to any particular number of choices. The check marks that he makes will determine the laboratories and branches to which his application will be circulated at the National Institutes of Health.

After thorough review of all applications by the Institutes, a limited number of candidates will be selected for personal interviews. NIH will pay air fare of those selected for interviews who elect to apply for Staff Fellow (civilian) appointment.

The NIH Associate office will set up the interviews and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

PART THREE

Program Areas for Which Candidates May Apply

Each of the major NIH components has prepared a description of its program areas for which Associates may seek appointment. Due to diversity of the operations and programs within these major components, the descriptions do not follow a pattern. In effect, however, all of these descriptions are meant to anticipate the questions which applicants may have in selecting the program areas for which they wish to be considered. It should be noted that a candidate is not limited as to the number or kinds of positions for which he may apply.

National Cancer Institute

Frank J. Rauscher, Jr., Ph.D., Director
Vincent T. DeVita, Jr., M.D., Clinical Director

Laboratories and Branches

- Director, Division of Cancer Biology and Diagnosis, Alan S. Rabson, M.D.
  - Associate Director for Program Planning, Irvin C. Plough, M.D.
    - Chief, Laboratory of Biochemistry, Robert F. Goldberger, M.D.
    - Chief, Laboratory of Cell Biology, Lloyd W. Law, Ph.D.
    - Chief, Laboratory of Immunodiagnosis, Ronald B. Herberman, M.D.
    - Chief, Laboratory of Molecular Biology, Ira H. Pastan, M.D.
    - Chief, Laboratory of Pathology, Louis B. Thomas, M.D.
    - Chief, Laboratory of Pathophysiology, Pietro M. Gullino, M.D.
    - Acting Chief, Laboratory of Theoretical Biology, Mones Berman, Ph.D.
    - Chief, Dermatology Branch, Marvin A. Lutzner, M.D.
    - Chief, Immunology Branch, William D. Terry, M.D.
    - Chief, Metabolism Branch, Thomas A. Waldmann, M.D.
- Director, Division of Cancer Treatment, Vincent T. DeVita, Jr., M.D.
  - Acting Deputy Director, Saul Schepartz, Ph.D.
  - Clinical Director, Vincent T. DeVita, Jr., M.D.
  - Deputy Clinical Director, John L. Ziegler, M.D.
  - Clinical Oncology Program, Vincent T. DeVita, Jr., M.D.
    - Chief, Medicine Branch, Robert C. Young, M.D.
    - Chief, Pediatric Oncology Branch, Arthur S. Levine, M.D.

Chief, NCI-VA Medical Oncology Branch, John D. Minna, M.D.
Chief, Radiation Oncology Branch, Ralph E. Johnson, M.D.
Chief, Surgery Branch, Steven A. Rosenberg, M.D.
Cancer Therapy Evaluation Program, Franco Muggia, M.D.
Chief, Investigational Drug Branch, Milan Slavik, M.D.
Chief, Combined Modality Branch, Franco Muggia, M.D.
Special Assistant, Clinical Investigations Branch, Hugh Davis, M.D.
Experimental Therapeutics Program, Vincent T. Oliverio, Ph.D.
Chief, Laboratory of Chemical Pharmacology, Richard A. Adamson, Ph.D.
Chief, Laboratory of Toxicology, Anthony M. Guarino, Ph.D.
Chief, Laboratory of Molecular Pharmacology, Kurt W. Kohn, M.D., Ph.D.
Chief, Laboratory of Tumor Cell Biology, Robert C. Gallo, M.D.
Drug Research and Development Program, Vincent T. Oliveria, Ph.D.
Chief, Laboratory Research, Abraham Goldin, Ph.D.
Chief, Drug Development Branch, Harry B. Wood, Jr., Ph.D.
Chief, Drug Evaluation Branch, John M. Venditti, Ph.D.
Acting Chief, Laboratory of Experimental Chemotherapy, Abraham Goldin, Ph.D.
Acting Chief, Laboratory of Medicinal Chemistry & Biology, David D. Johns, Ph.D.
Baltimore Cancer Research Center, Michael D. Walker, M.D.
Chief, Laboratory of Pharmacology, Carl C. Levy, Ph.D.
Chief, Clinical Branch, Michael D. Walker, M.D.

Division of Cancer Biology and Diagnosis

A broad range of research is carried out in both basic laboratories and clinical branches under the general direction of Dr. Alan S. Rabson.

The Laboratory of Biochemistry consists of six sections. The Cellular Regulation Section is concerned with the molecular mechanisms by which steroid hormones regulate specific gene expression in eukaryotes. The system under investigation is egg yolk phosphoprotein synthesis in the liver of the rooster after treatment with estrogen. This system has the advantages of a hormonal response that is highly specific and of great magnitude in a tissue capable of a wide diversity of genetic expression. The approach involves studies with purified components *in vitro* as well as with cultured cells and whole animals.

The Nucleic Acid Enzymology Section is concerned with the study of nucleic acid metabolism and structure. Systems under study include the replication of Simian Virus 40 DNA in permissively infected monkey cells; the structure and origin of defective Simian Virus 40 DNA containing host DNA sequences; bacterial polynucleotide phosphorylase; cyclic AMP metabolism; the role of histone 1 in chromatin structure. Emphasis is placed on reaction mechanisms by two main approaches: (1) structure of substrates and products; and (2) relation of protein structure to function.

A variety of modern techniques of nucleic acid and protein chemistry are employed.

The Biochemistry of Gene Expression Section studies control of gene expression in eukaryotic cells and its application to clinical medicine. The effects of steroid hormones on enzyme induction both in cultured cells and cell hybrids are investigated, along with studies on steroid receptors in human leukemia and breast cancer. Techniques of cell culture, cell fusion, chromosome banding, protein synthesis, and affinity chromatography are among those utilized.

The Biosynthesis Section currently conducts research on the regulation of collagen biosynthesis, the molecular properties and function of eukaryotic DNA polymerases, the transcription of covalently linked host and viral (SV40) genetic information, and the regulation of cell surface configuration (using correlated electron microscopic and metabolic studies).

The Cell Physiology and Oncogenesis Section investigates cellular and molecular events in the neoplastic transformation of mammalian cells in culture. The goals of this section include early detection of neoplastic transformation and elucidation of the cause and effect relationships in oncogenesis. Among the tools employed are long-term tissue culture, modern biochemical methods, animal transplantation, microscopy-photography, and radioisotopic techniques.

The Protein Chemistry Section is investigating biochemical changes accompanying the maturation of granulocytes in bone marrow, interactions between cells involved in the immune response, and the transfer of genetic information through the cellular uptake of isolated chromosomes. Tissue culture, protein fractionation, cell separation and radioisotopic procedures are employed.

Personnel of the Laboratory of Cell Biology have diverse interests focusing upon the study of transformation of a normal cell to a neoplastic cell. Techniques from the fields of virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization, and electron microscopy are used. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells (principally plasma cells), role of cell membranes in regulating differentiation and growth, identification and study of tumor antigens and of the specific immune reactions initiated, solubilization and purification of transplantation and tumor antigens, influence of somatic cell hybridization on expression of genetically determined events, and ultrastructural analysis and molecular biology of viral oncogenesis.

The Laboratory of Immunodiagnosis conducts studies on the nature of tumor associated antigens and other cell surface antigens on tumor cells and on the immune response to these antigens. The antigens in several tumor systems, both in animals and in man, are being studied, particularly in regard to their role in host resistance against tumor growth and their possible diagnostic applications. The cell-mediated and humoral immune responses to a variety of experimental and human tumors are being extensively studied. The assays for cellular immunity include radioisotopic and visual cytotoxicity assays, lymphocyte stimulation, migration inhibition, and skin tests for delayed hypersensitivity. The interrelationships among these assays and the usefulness of each for the diagnosis of cancer and for monitoring of tumor-bearing individuals are being investigated.

The program offers the opportunity to perform research in experimental tumor systems and/or to perform immunologic investigations on patients with cancer.

The LABORATORY OF MOLECULAR BIOLOGY investigates cell behavior, gene function, and other regulatory mechanisms in animal and bacterial cells.

Particular attention is given to the identification and isolation of regulatory molecules and to studies on the mechanism of action of these substances.

Cells transformed by oncogenic viruses as well as physical and chemical agents have alterations in cell shape, adhesiveness, motility, surface structure and growth control. Transformed cells are used to investigate the nature of molecules that control these phenomena. Special attention is now focused on two molecules, cyclic AMP and CSP, that have a role in regulation of cell behavior and are often decreased in transformation. Cyclic CSP is a large molecular weight cell surface protein. Mutants defective in adhesion, motility and growth control are isolated and used for biochemical analysis, with particular attention to contractile proteins and proteins associated with the plasma membrane. Other efforts are directed towards elucidating the viral gene products responsible for the initiation of transformation. The mammary tumor system in mice is being studied, particularly to elucidate the morphology and biochemistry of the virus particle, and to identify various lines of the virus. Regulation of oncornaviral expression in mammalian cells is studied by inducing viral replication through cell hybridization and chromosome segregation.

Factors regulating the organization of subcellular organelles in cells, their position, number, and turnover rates, and how they cooperate in cell function are under investigation. Processes such as cell growth, macropinocytosis, exocytosis, and transport of proteins within cells are of particular interest. Finally, investigations are being carried out on how cells interact in organ growth and function.

The regulation of prokaryotic gene expression is studied using cell-free systems containing purified proteins and specific bacterial and viral genes. Mutants defective in initiation and termination of transcription are isolated and employed to detect new regulatory compounds or to elucidate regulatory mechanisms. The nucleotide sequence of genetic regulatory regions is under intensive study.

Other efforts are directed towards investigating the molecular basis of genetic recombination. The studies use the bacteriophage λ and its host, *E. coli*. Mutants defective in recombination are isolated and the nature of their defects analyzed by both genetic and biochemical methods.

The LABORATORY OF PATHOLOGY of the National Cancer Institute offers a 2-to-4-year training program for residents in pathologic anatomy in the Clinical Center, National Institutes of Health, Bethesda, Maryland. The program, which is fully approved for Board certification, provides well supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. Opportunity is provided for learning many research techniques, particularly electron microscopy, fluorescence microscopy, tissue culture, histochemistry, autoradiography, and cytogenetics. Individual or collaborative participation in clinical or laboratory research projects by the residents and selected Research Fellows and Visiting Scientists is encouraged.

In addition to the autopsy, surgical pathology, and cytodiagnostic services, the laboratory also carries on a broad research program in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

Laboratory of Pathophysiology. The Section on Cellular and Molecular Physiology studies the biochemical mechanisms which control the early stages of cell growth induction in normal and neoplastic human cells. Emphasis is on the mechanisms which maintain physiologically resting cells in the non-growing condition and the early biochemical modifications which occur on growth stimulation. Current studies include characterization of translational controls in resting human lymphocytes, examination of facets of messenger RNA metabolism which are unique to physiologically resting cells, and studies of the regulation of the production of specific proteins whose synthesis is related to the onset of lymphocyte growth.

The Section on Cell Cycle Regulation is concerned with the characterization of biological events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the synthesis of oligo (ADP-ribose), the activity of the enzyme complex synthesizing the oligomer, and the effect of a change in its concentration on the cell cycle.

The Section on Membrane Biology carries on work in the field of freeze-fracture of plasma membrane with particular emphasis on intramembranous particles, their aggregation and biological significance.

The Section on Nucleic Acids is studying the differences between nuclear and cytoplasmic DNA in an effort to characterize the chemical and physiological roles of DNA in mitochondria, melanin, and zymogen granules.

The Section on Energy Metabolism is concerned with the physiological and behavioral control of food and water intake and its relation to cancer cachexia.

The Section on Radiation Biology is involved in the use of radiation to destroy bone marrow and to study the laws governing marrow transplantation from donors. The effects of ionizing and UV radiation on nucleic acids and proteins are also being studied.

Finally, a group of projects concerning the process of mammary tumor regression, the role of hormonal deprivation of the host on cell survival, and the effect of cAMP on the initiation and progression of tumor regression, is carried on in collaboration with the Office of the Chief.

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The LABORATORY OF THEORETICAL BIOLOGY is concerned with the formulation of theories of structure, function, and dynamics of biological systems and with the development of mathematical and computational techniques for the analysis of those systems. Several areas are of particular interest. These include the development of formal models for the kinetics of metabolites, therapy agents, and hormonal regulation, membrane structure and function, transport through artificial lipid bilayer membranes, the configurations and properties of polypeptides and other macromolecules, immune response systems, and surface receptors. Although the work is predominantly theoretical, experimental studies related to these problems are carried out within the laboratory and in collaboration with others.

The DERMATOLOGY BRANCH studies growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic and neoplastic states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; T cell leukemias (Sezary syndrome and mycosis fungoides); and physiology of lymphoreticular cells and lymphokine formation.

Other studies include experimental allergic contact dermatitis in man; scanning and transmission electron microscopy of the ultrastructure of normal and diseased skin and other tissues; scanning microscopy of the surface structure of cells in relation to the mitotic cycle and motility; genodermatoses; biochemical and ultrastructural aspects of melanogenesis in normal and melanoma tissue; biochemistry of keratinization; xeroderma pigmentosum—an inherited disease of sun sensitivity and multiple cutaneous cancers with abnormal DNA repair (complementation, mutagenesis and carcinogenesis); chemical and ultrastructural effects of Vitamin A on skin; potential oncogenic skin viruses; the development of therapy of epithelial cancers, skin lymphomas, and certain benign diseases of the skin.

The Branch is staffed by dermatologists, virologists, biochemists, and morphologists and immunologists active in the training of clinical and basic researchers. One year's credit towards Board certification in dermatology can be offered for time spent in the two year clinical associateship program. Clinical Associates may remain for a 3rd and/or 4th year to complete research projects.

In the IMMUNOLOGY BRANCH, clinical and basic science approaches are combined in the study of immune responses to normal and malignant cell surface antigens. Fundamental investigations stress mechanisms of normal and disordered immune responses and modes of specifically modifying those responses. Immunochemical, biochemical, serologic, immunogenetic, and tissue culture techniques are applied to research on the structure and function of antibodies and cell surface receptors and the genetic control of immune responses. A variety of animal models is used in the study and characterization of histocompatability antigens, differentiation antigens, tumor specific antigens, and cell surface antigens of possible importance in cellular cooperation. Clinical interests include immunotherapy of malignant disease, transplantation immunology, and *in vitro* correlates of immunity in disease states and during therapy.

The METABOLISM BRANCH has two major areas of clinical research, the first in clinical immunology and the second in clinical endocrinology and metabolism. The clinical and laboratory programs in immunology cover a broad range of immunological problems, especially as they involve immunodeficiency states in man associated with a high incidence of malignancy. The studies are concerned with the nature of the abnormalities of circulating and cellular immune responses in animal models and in patients with such disorders as agammaglobulinemia, the Wiskott-Aldrich syndrome, ataxia telangiectasia, multiple myeloma, chronic lymphocytic leukemia, intestinal lymphangiectasia, gluten-sensitive enteropathy and autoimmune diseases. Special attention is given to the role of abnormalities of suppressor cells in the pathogenesis of immunodeficiency, the role of macrophages in antigen processing and recognition, the factors controlling the differentiation of lymphoid cells, cell-surface membrane markers of lymphoid cells, the function of effector or killer cells and the relationship between human disease, and the immune response and histocompatability genes.

The second area of emphasis, clinical endocrinology and metabolism, involves the study of metabolic derangements of the homeostatic control mechanisms with special emphasis on the study of porphyrin metabolism, collagen metabolism, and hormonal control of growth. Patients with derangements of porphyrin metabolic pathways are studied in investigations of the factors regulating porphyrin biosynthesis. The regulation of the enzymes of pyrroline and collagen metabolism is studied in patients with genetic and acquired defects of collagen and bone metabolism. The mode of action of growth hormone and somatomedin in the biochemical events accompanying normal and disordered growth is being investigated.

The candidates for Clinical Associates on the Metabolism Branch ultimately apply for a position with a specific investigator on a program either in the immunological or endocrinological and metabolic areas of the Branch. Throughout the two years the Clinical Associate will be involved in both laboratory and clinical investigations as well as clinical care of patients with illnesses related to his own research interests and those of his Senior Investigator. The goal of the training program is to provide the associate experience in both the techniques of clinical research as well as in either of the clinical superspecialty areas of clinical immunology and allergy or endocrinology and metabolism.

Division of Cancer Treatment

An intensive program of laboratory research and clinical investigation concerned with the therapy of cancer is under the direction of Dr. Vincent T. DeVita, Jr.Emphasis is placed on combinations of drugs with other modalities of therapy including surgery, radiation, and immunotherapy.

THE CANCER THERAPY EVALUATION PROGRAM is involved in monitoring clinical trials with investigational and known antineoplastic treatment modalities. The scope of the program has evolved from broad drug trials with investigational chemotherapeutic agents to disease-oriented approaches including incorporation of effective drug combinations during early stages of disease and testing of new modalities, such as immunotherapy, in combination with surgery, radiotherapy, and chemotherapy in specific diseases that were until now considered untreatable. With the new responsibility for coordinating activities in the cooperative oncology groups, the program is setting up meetings with representatives from all interested groups and institutions throughout the nation. Evaluation of effectiveness of types and methods of cancer therapy, and dissemination and exchange of information on clinical trials are also important aspects of the program.

The CLINICAL INVESTIGATIONS BRANCH is responsible for monitoring the activities of the cooperative oncology groups, including critical review of protocols and updating of information on clinical trials within and outside the group programs. The Branch serves as liaison between the National Cancer Institute and group investigators throughout this country and others.

The COMBINED MODALITY BRANCH implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide specific and immediate clinical trials of combined modality approaches to the therapy of specific tumors. It is responsible for bringing together, under contract, expertise in chemotherapy, surgery, radiotherapy, and immunotherapy in the design of comprehensive therapeutic programs geared to the eventual cure of specific disease entities. It is responsible for maintaining continuing liaison with various advisory and consultant groups established as working committees to study the effectiveness of specific types and methods of cancer therapy.

The INVESTIGATIONAL DRUG BRANCH implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide highly specific and immediate clinical trials of anticancer drugs that have demonstrated high activity in animals in the preclinical phase of the drug development aspect of the Cancer Therapy Program. The Branch is responsible for the communication and filing of all information required by the Food and Drug Administration in connection with the Drug Development Program of the National Cancer Institute.

The CLINICAL ONCOLOGY PROGRAM consists of the Medicine Branch, the Pediatric Oncology Branch, the Radiation Oncology Branch, the Surgery Branch, and the NCI-VA Medical Oncology Branch.

The MEDICINE BRANCH is a medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of malignant lymphomas, breast cancer, ovarian carcinoma, sarcomas, melanoma, cancer of the pancreas, chronic leukemias, and myeloproliferative disorders. Training in clinical diagnostic procedures related to cancer, such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH including cancer surgery and radiation therapy. The Branch conducts weekly clinical conferences with the departments of Radiation Oncology, Pathology, Clinical Pathology (Hematology), and Radiology on current problems and on the staging of lymphomas. The research program focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. Collaboration with the Laboratory of Chemical Pharmacology and other groups concerned with marrow culture is maintained.

In addition, an active research program is maintained in the field of hormone receptors, tumor markers, and tissue culture.

The PEDIATRIC ONCOLOGY BRANCH practices a combined modality approach to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, neuroblastoma, aplastic anemia, and histiocytosis. Children and young adults are accepted for treatment. Three areas of clinical investigation are stressed: (a) chemotherapy and immunotherapy; (b) hematologic support and bone marrow transplantation; and (c) diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The Branch is particularly interested in the psychosocial aspects of cancer, and training in this area is emphasized. Candidates with prior training in medicine or in pediatrics may apply to this Branch and may be Board eligible in medical oncology or in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical means followed by chemoimmunotherapeutic manipulations, the goal of which is significant prolongation of remission. Comprehensive immunological assays are performed in order to assess the utility of various techniques in understanding the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. A major area of interest is hematologic reconstitution through allogeneic, isogeneic, and autologous bone marrow transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised host. These maneuvers include the use of laminar-air-flow isolation and prophylactic antimicrobial agents. Studies on microdetermination of circulating endotoxin and on the molecular identification of latent viral genetic material illustrate newer diagnostic approaches to infectious disease.

In the second year of this program, clinical research training is offered in the three areas previously described. In addition to clinical research, this Branch has a strong program in basic laboratory investigation with emphasis on the molecular biology of tumor viruses, tumor cell biology, molecular and clinical pharmacology, tumor immunology, somatic cell hybridization, and immunohematology. Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates, utilizing excellent collaborative relations with other Branches of the NIH.

The RADIATION ONCOLOGY BRANCH has a multidisciplinary orientation with a staff consisting of radiotherapists and medical oncologists. The clinical emphasis is on combined modality approaches in cancer therapy. Training includes not only experience with chemotherapy but with various diagnostic procedures, including bone marrow and liver biopsy, peritoneoscopy, and fiberoptic bronchoscopy. The two-year program includes nine months of ward (inpatient) assignment and rotations through radiation therapy, tumor pathology, surgical oncology, and immunology. A six-month period without specific assignment is provided to allow for election of additional training in any particular clinical area(s) or experimental laboratory investigation. There is continuous outpatient care of selected patients during the entire two years to insure the opportunity for longitudinal observation and management. Finally, while the clinical research programs of the Branch concentrate on specific diseases, experience is gained with a wide spectrum of malignancy by virtue of collaborative studies with other Branches, through rotations, and by assignment to an oncology consultation service.

The SURGERY BRANCH is a surgical oncology unit emphasizing a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen including melanomas, sarcomas, rectal cancers, pancreatic cancers, and head and neck cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy as well as the development of new surgical techniques. The laboratory efforts of the Surgery Branch are closely related to its clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The Branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, x-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch staff also serve as general surgeons to the entire National Institutes of Health and see a variety of general surgical consultations not related to the field of cancer.

The NCI-VA MEDICAL ONCOLOGY BRANCH is located outside the Clinical Center at the Veterans Administration Hospital in northwest Washington, D.C. This Branch is concerned with the primary care and clinical investigation of patients with a wide variety of solid tumors and hematologic malignancies. A major effort involves the staging and treatment of small cell carcinoma of the lung. In addition to lung cancer, treatment protocols of head and neck, stomach, pancreatic, colorectal, and prostatic carcinoma are underway. Associates become experienced in diagnostic procedures, such as bone marrow biopsy, liver biopsy, fiberoptic bronchoscopy, and peritoneoscopy. Programs in the treatment of both acute and chronic leukemias, myelomas, lymphomas, and premalignant hematologic syndromes are being developed with the Division of Hematology. Both veteran and nonveteran patients are admitted for study, and the Branch provides oncology consultation for the hospital.

The Branch laboratory investigations in human tumor cell biology involve studies of oncogenic viruses, molecular biology, cell culture, somatic cell hybridization, and human tumor cell genetics and cytogenetics. *In vitro* models for chemotherapy are under study and clinical investigation of tumor cell kinetics is carried out. The fellowship program is designed to include both clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals. To further this end, close ties and collaboration with the Clinical Center in Bethesda are maintained.

The EXPERIMENTAL THERAPEUTICS PROGRAM studies many facets of the interaction between drugs and living materials. It includes biochemical pharmacology, toxicology, physiological disposition, drug metabolism, molecular biology, mechanism of action, and comparative pharmacology. In addition, it works closely with the Medical Oncology Program with regard to clinical research problems.

The Office of the Associate Director, in addition to an overall administrative responsibility for four laboratories, conducts a research effort in the area of the exchange of various physiological and pharmacological substances between blood, cerebrospinal fluid, and brain extracellular and intracellular fluids. Both experimental and computer studies are designed to increase our understanding of the basic transport mechanisms involved in the system and to examine the delivery of drugs to normal tissue and tumor sites within the brain, spinal cord, and meninges. These efforts are intended to elucidate new and better routes of drug administration, find key physicochemical and structural properties of potential chemotherapeutic agents which will optimize tissue delivery, and develop ways to transiently modify the "transport barriers" and subsequently increase drug uptake. Another important area of research concerns biochemical pharmacology of antitumor drugs in preclinical systems, an effort which blends well with ongoing activities in the laboratories within the Experimental Therapeutics Program.

The LABORATORY OF TOXICOLOGY functions to investigate and describe the qualitative and quantitative toxicity of potential antineoplastic drugs using animal test systems. Young and old animals of both sexes, as well as pregnant animals are included in these studies. Treatments range from acute to chronic. Adverse effects of oncolytic agents in man are correlated with those observed in lower species in an effort to increase the predictability of the animal test systems. Attempts are made to define the predictability, reversibility, and mechanisms of drug-induced toxicity. The pathogenesis of the lesions detected is studied at every level from the morphologic to the molecular. Wherever possible, antidotes are sought. In order to achieve the greatest therapeutic effect at the least cost in serious side effects, a variety of experimental treatment regimens are tested. The Laboratory of Toxicology also investigates whether proposed drug combinations alter toxicity and therapeutic efficacy by evoking changes in drug binding, absorption, distribution, and/or metabolism. The Laboratory is composed of three scientific units: Biochemistry, Comparative Pathology and Drug Interactions. All the functions of the Laboratory are closely integrated with the development of new anticancer agents and ongoing clinical studies.

The LABORATORY OF MOLECULAR PHARMACOLOGY is engaged in fundamental studies on the mechanisms of drug action on mammalian cells, particularly actions involving nucleic acids and related structures. Of major interest are (1) interactions between drugs and macromolecules studied by physical chemical techniques, (2) effects on the synthesis and function of nucleic acids and related structures in cells, and (3) relations between molecular effects of drugs and their biological effects on cells. The drugs studied are actual or potential chemotherapeutic agents or compounds having special properties that facilitate relevant studies of intracellular processes.

The LABORATORY OF CHEMICAL PHARMACOLOGY is primarily engaged in studies of the pharmacology of new and established antitumor agents and other drugs used in patients with cancer. Clinical Associates assigned to this area spend their first year as primary physicians on the wards of the Medicine Branch. During the second year, they participate in laboratory research projects under the direction of a senior investigator in the Laboratory of Chemical Pharmacology. A wide range of research topics related to the pharmacology of antineoplastic agents is under active investigation. Particular emphasis is placed on the pharmacokinetics and cellular transport of the agents, the effect of the agents on the cell cycle, the disposition of antitumor agents in animals and man and the enzyme systems involved in the metabolism of the antitumor agents. Other studies include mechanisms of resistance to anticancer agents; structure activity relationships of antitumor agents; new approaches to cancer chemotherapy; the untoward effects of drugs resulting from inherent physical-chemical properties and/or interactions with other concomitantly used drugs; and biological markers which will aid in the diagnosis and treatment of the precancerous state as well as frank neoplasia. Agents of recent interest have been maytansine, inosine dialdehyde, gallium, alanosine, nitrosoureas, rifampicin analogs, interferon and interferon-inducers, carboxypeptidase G_1, DNA and RNA binding antibiotics, hycanthone, and the folic acid antagonists. Biological markers of recent interest have been alpha-fetoprotein, carcinoembryonic antigen, methylated nucleic acid bases, HCG, polyamines, and sialic acid. In all areas of interest, both fundamental and pragmatic approaches are utilized.

The LABORATORY OF TUMOR CELL BIOLOGY has several major research interests including studies on: (1) the controls of cellular growth, differentiation, maturation, and the process of malignant transformation in mammalian cells; (2) mechanism of action of new antitumor agents and elucidating alterations involved in the development of resistance to drugs; (3) development of molecular probes for the presence of small numbers of neoplastic cells; (4) purification and biochemical and biological characterization of DNA polymerases from human cells and from oncogenic RNA viruses ("reverse transcriptase" or RNA-dependent DNA polymerase). These studies are designed to aid in the understanding of the function of these enzymes, *e.g.*, appearance in the cell cycle, activity with certain compounds, role in cellular differentiation, and role in neoplastic transformation. The questions of whether any of the enzymes in cells are viral in origin and whether DNA and RNA polymerases of neoplastic cells differ qualitatively or quantitatively from those of normal cells are under intense study; (5) development of new molecular probes for virus specified information in cells; (6) new antiviral agents are evaluated in a number of biological and biochemical systems; and (7) attempts to elucidate the origin and evolution of RNA tumor viruses and if information from these viruses is involved in the etiology of human neoplasias. Overall the major goals may be summarized as attempts to develop new approaches for diagnosis, prognosis, and therapy of human neoplasia based on information derived from basic studies on neoplastic cells and on the conversion *in vitro* of normal cells to neoplastic cells.

The DRUG RESEARCH AND DEVELOPMENT PROGRAM is engaged in a multidisciplinary approach to the fundamental and developmental aspects of cancer chemotherapy. Through contracts and direct laboratory operations it carries out programs directed toward the development of new and better antitumor agents.

The LABORATORY RESEARCH PROGRAM within the immediate office involves correlation of fundamental laboratory investigations with preclinical developmental and clinical investigations. Surveillance of research and new drug development is undertaken on an international scale and includes maintenance of chemotherapy offices in Europe and Japan. Selected collaborative research programs are concerned with fundamental chemotherapeutic, biological, biochemical, and immunological investigations of the mechanism of action of antitumor and antiviral agents, new therapeutic models, metastasis, drug resistance, combined modalities, animal genetics and disease control.

The DRUG DEVELOPMENT BRANCH is responsible for the development of more effective chemical agents for human cancer chemotherapy, primarily through contract-supported projects. New agents are prepared by laboratory synthesis or derived from modified natural products. Active compounds may be modified to broaden and increase their therapeutic effectiveness and to lessen their toxicity. Theoretical designs, particularly for drugs that may be useful for the slower growing or organ specific tumors, are explored. Research efforts are also directed towards the analysis of structure-activity patterns. Computer-assisted programs for chemical data processing and information storage and worldwide search for potential antitumor agents are also implemented by the Branch. A literature surveillance program is being developed for selecting reported compounds of interest to use in cancer treatment. Methods for preselecting compounds with greater-than-average probability for broad spectrum activity are being developed.

The DRUG EVALUATION BRANCH is engaged in a broad approach to the recognition of potential new anticancer drugs and to fundamental and developmental aspects of antitumor therapy. Studies include: testing of unknown materials for biological activities of predictive value to the clinic; detailed evaluation of drugs as potential clinical candidates with respect to optimal usage, including treatment route and schedule, combination chemotherapy, and combined treatment modalities; mechanisms of drug action and other biochemical and cellular kinetic aspects of cancer chemotherapy; the investigation of specific problems that emerge from toxicological studies in large animals or in early clinical trial; mechanisms of drug resistance and means of overcoming resistance; establishment of new therapeutic principles and procedures for the management of tumor growth in animals; structure-activity relationships; the development of new and improved *in vivo* and *in vitro* assays for drug evaluation including disease-oriented tumor models; the development and use of computer systems for processing the data generated.

The LABORATORY OF EXPERIMENTAL CHEMOTHERAPY undertakes fundamental studies of the biology of normal and tumor cells in chemotherapy; investigation of the fundamental basis of drug specificity; study of sensitivity differences and control mechanisms in the cell cycle; basis and therapy of invasiveness and metastasis; rational modification of structural analogs and structure-activity analysis, study of the basis of resistance and cross-resistance to antitumor agents; development of new models for drug evaluation; combination chemotherapy; surgical adjuvant chemotherapy; radiation plus chemotherapy; investigation of host immunological factors in tumor growth; studies of the combined effects of immunity and chemotherapy involving active, passive, adoptive or nonspecific types of immunotherapy; antigenic alteration plus chemotherapy in relation to collateral sensitivity. The studies are correlated with the clinic in the development of modalities of therapy, special problems, and therapeutic principles.

The LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY conducts an integrated program for the development of new antitumor agents. The synthesis of compounds with potential antitumor activity is carried out, and the effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo*, and on a variety of subcellular target sites, e.g., nucleic acids, cell membranes, microtubular protein enzyme systems. Flexibility in the development of new biological test systems of predictive value to the medicinal chemistry program is emphasized. The Laboratory develops analytical methodology for *in vivo* studies with new agents, and, where warranted, extends biological studies with such agents to the preclinical and initial clinical Phase I stages. In addition, the Laboratory manages a contract-supported program to characterize the mode of action of new antitumor agents at the molecular and cellular level. The Laboratory stresses the rapid and continuous utilization of the data generated from intramural and collaborative biological studies for the elucidation of structure-activity correlations and for guidance in the synthesis of new antitumor agents of potential clinical value.

The BALTIMORE CANCER RESEARCH CENTER, which occupies the entire ninth floor of 3 adjacent buildings at the University of Maryland Hospital, is engaged in laboratory and clinical cancer research. The Clinical Oncology Branch operates a 40-bed inpatient and large outpatient facility. The Branch is engaged in research on the treatment of various malignant diseases, such as leukemia, lymphoma, metastatic solid tumors, and brain tumors. In addition, research on supportive care of patients with malignant diseases is carried out. Studies of granulocyte and platelet procurement, storage, and transfusion are currently in progress. Studies of laminar air flow rooms and other methods of providing the granulocytopenic patient with a protected environment are also under investigation. Newer, potentially useful methods of cancer treatment, such as hyperthermia, are also under active investigation. The Clinical Oncology Program is approved by the American Board of Internal Medicine for credit toward certification in Internal Medicine and the subspecialty of Medical Oncology.

The Center's Laboratory consists of sections of Enzymology, Biochemistry, Microbiology, Immunology, and Neuropharmacology. The Enzymology Laboratory is currently engaged in nucleic acid research, and the Biochemistry Laboratory conducts clinical pharmacokinetic studies of new anticancer drugs. The Microbiology Laboratory studies new antibiotics and performs epidemiological and viral studies. Basic and clinical immunological investigations are performed by the Immunology Laboratory, and the Neuropharmacology Laboratory is engaged in many aspects of brain tumor research. Second year clinical associates may do basic or clinical research in one of these areas.

The LABORATORY OF PHARMACOLOGY (Dr. Carl Levy, Chief) is concerned with basic and applied research programs in biochemical pharmacology, drug metabolism, molecular biology, and cancer immunology and metabolism. The SECTION OF BIOCHEMISTRY (Dr. Nicholas Bachur, Head) studies controls of cellular growth and differentiation and mechanisms for exogenous control (i.e., drugs). Particular interest is directed to clinical biochemical problems and problems of clinical pharmacology. The SECTION OF ENZYMOLOGY AND DRUG METABOLISM (Dr. Carl Levy, Head) studies drug enzyme interactions in a program attempting to elucidate various markers of cancers. In addition, the Section is concerned with therapeutic agents affecting cellular proliferation characteristics. The SECTION OF IMMUNOLOGY AND CELL BIOLOGY (Dr. Michael R. Mardiney, Jr., Head) is involved with studying basic and applied aspects of host immune modulation with particular emphasis on cancer immunology. Programs involving the mechanism of adjuvant activity upon the immune response, as well as the development of techniques for monitoring host immunity to tumor are being carried out.

National Eye Institute

Carl Kupfer, M.D., Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three Clinical Associates from those candidates who have completed an accredited 3-year ophthalmology program. Clinical Associates spend time in both clinical and laboratory research, including patient care activities.

In selection of Clinical and Research Associates, preference will be given to those who will continue their research training either at the

National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

Laboratory and Clinical Research

The National Eye Institute has developed its clinical and research program into two major branches, the Laboratory of Vision Research and the Clinical Branch. The Laboratory of Vision Research plans and conducts fundamental laboratory research on the visual system. This includes anatomy, biochemistry, physiology, embryology, pharmacology, and experimental pathology of the visual system.

The CLINICAL BRANCH plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of disorders of the visual system. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the Clinical Branch's responsibility to investigate the causes and prevention of blindness. The major areas under study are cataracts of unusual origin, glaucoma, neuro-ophthalmology, ophthalmic genetics, vascular diseases, retinal degenerations, and ophthalmic pathology.

(1) Cataracts of unusual origin are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

(2) Neuro-ophthalmology: Patients from the ophthalmic and neurologic services are being studied using advanced methods for electro-oculography, pupillometry, video tape recording, and computer analysis. The main emphasis of these studies at present is on cerebellar disorders that affect ocular movements.

(3) Glaucoma: Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is underway.

Innovative surgical techniques are being assessed in selected cases of hemorrhage and congenital glaucoma and in cases in which anti-glaucoma surgery has failed.

Axoplasmic flow is being studied in optic nerves of glaucomatous monkeys, and the properties of trabecular meshwork are being studied in tissue culture.

(4) Ophthalmic genetic studies include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogeneses of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

(5) In vascular diseases, investigations are being conducted to define underlying mechanisms in conditions such as diabetic retinopathy, macular degenerations, and other retinal vascular diseases or vascular disease of the optic nerve. A controlled clinical trial of anti-coagulation and thrombolytic agents in occlusion of the central retinal vein is underway.

(6) Ophthalmic Pathology: Eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied histopathologically and electron microscopically. Many of these eyes are from subjects who have rare or unusual metabolic diseases or who have been subjected to prolonged courses of anti-cancer treatment. There is opportunity for close collaboration with investigators in the Laboratory for Vision Research in the Eye Institute.

The LABORATORY OF VISION RESEARCH is composed of the following disciplines:

(1) BIOCHEMISTRY. This section is conducting studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolisms of photoreceptors are also under investigation. Finally, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

(2) EXPERIMENTAL EMBRYOLOGY. The goals of this section are to identify and characterize the myriad tissue interaction that controls the orderly growth of the vertebrate eye and to assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the species and tissue specificities of these interactions, and the nature of these tissue interactions which control morphogenesis.

Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. In particular, attention is being focused on newly discovered, cell-free, collagen containing "interior layers" that are transiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

(3) EXPERIMENTAL PATHOLOGY. Research being conducted in this section of the laboratory centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

(4) NEUROPHYSIOLOGY. Investigations in this section are currently underway to better understand the cellular organization underlying visual perception in both health and disease. Studies are being conducted on the responses of single nerve cells in the visual nervous system of the rhesus monkey. The purpose of this work is to understand how each nerve cell functions in contributing to visual sensations such as color, shape, movement, depth, etc. The technique employs fine glass micro-electrodes which can be inserted into the brain in order to record from single nerve cells. It

uses refined optical methods to enable an experimenter to observe the retina while stimulating it with punctate spots or lines of colored lights whose movement and shape can be quantitatively controlled. It requires electrophoresing particles of dye into single cells whose responses have been studied and then finding these particles precisely within the brain after the animal is sacrificed.

Studies in the rhesus monkey striate cortex, which have indicated that visual information processing by the brain involves feature detection rather than photographic reproduction, also include investigations of retinal function at the cellular level. The goal is to better understand vision and pathophysiology of retinal disease. Deeper understanding of abnormal states in the cellular physiology of the mammalian retina is also expected to emerge from studies in this section.

(5) RETINAL AND CORNEAL METABOLISM. Members of this section are investigating the function of the retina, pigment epithelium, and cornea in relation to clinical diseases such as retinitis pigmentosa and keratomalacia.

The mechanism by which visual cells detect light and produce neural messages is not known. Calcium may play a role in the process since it mimics the effects of light on the retina and is found in very high concentrations in pigment epithelium and retinal photoreceptors. Small intracellular messengers called cyclic nucleotides have also been found in extraordinarily high concentrations in retinal photoreceptors. Since light markedly affects their concentration, they, too, are probably intimately involved in the visual process. A method of injecting various substances into visual cells is now being developed to determine directly the effect of these substances on the visual process in both normal and pathologic conditions.

Studies on the synthesis and degradation of the visual protein rhodopsin have helped explain how retinal photoreceptors are renewed. Defects in this process may underlie some forms of retinal degeneration; thus, studies using dystrophic retinas of test animals are underway to compare the process of photoreceptor renewal in normal and pathologic conditions. Substances such as hormones and neurotransmitters which affect the normal growth and development of retinal cells in tissue culture are being assessed. Several of these have already been identified and are being further studied in relation to their role in retinal function.

Specific receptor molecules for vitamin A have been found in retina and pigment epithelium. These receptors are probably involved in the normal uptake, distribution and retention of the vitamin in the visual system. Differences in receptor concentrations in retinas of normal humans and patients with retinitis pigmentosa have been found.

Vitamin A receptors are also present in the cornea and conjuctiva. The possible relationship of these receptors to corneal disease is being considered. Other aspects of corneal physiology, such as glutathione metabolism, are under investigation. Such studies are important not only for understanding corneal function and transparency but for improving corneal transplant and surgery techniques as well.

National Heart, Lung, and Blood Institute

Jack Orloff, M.D., Director of Intramural Research
Harry R. Keiser, M.D., Clinical Director

Associate Program in Medicine Surgery and the Basic Sciences

The National Heart, Lung, and Blood Institute currently appoints three Research Associates and six Clinical Associates in Medicine for a 2-year period beginning each July 1. Several Staff Associates are also appointed in one or more of the Institute's laboratories. For those who are interested in lengthening their period of research experience, these appointments may usually be extended, by mutual agreement, for a third year. Four to five Clinical Associates are also appointed for 2-year periods in Surgery.

Research and Clinical Associates in Medicine

Candidates for Research and Clinical Associate positions have only one interview in this Institute. Associates are interviewed by a committee made up of the Director of Intramural Research, the Clinical Director, and a Chief of one of the Institute's laboratories or branches. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the NHLBI. After appointment and prior to entering on duty, each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the Associate and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. (On the basis of past experience, it appears virtually certain that each Associate will be able to work with the group of his choice.) The level of research responsibility and freedom will depend upon his training and experience as well as his desires.

Each Associate in medicine will devote his time primarily to research in the laboratory under the immediate supervision of a preceptor in an area of his selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of his laboratory.

RESEARCH ASSOCIATE. These appointments are designed to give physicians an opportunity to improve their background for a career in basic medical research. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. No clinical assignments are involved (unless the Associate has chosen a laboratory involved directly in clinical investigation), but the Associates are welcome to attend any of the clinical teaching exercises.

CLINICAL ASSOCIATES. These appointments are designed to give physicians training in both clinical and basic research. Candidates must have completed a minimum of 1 year of internship plus 1 year of residency in internal medicine by the starting date of their appointment.

Clinical Associates will be responsible, under the guidance of investigators on the Heart, Lung, and Blood Institute staff, for the medical care of patients during 10 of the first 12 months of their service. During this time they will rotate through the three medical services that serve the clinically oriented branches of the Institute. These services occupy 75 beds and include: (1) Cardiology, (2) Endocrinology-Hypertension, and (3) Metabolism, Hematology and Lung.

The clinical period is one of intensive training under direction of the Clinical Director and staff. It offers exposure to case material of an extraordinary range and to highly sophisticated approaches to investigation of disease.

The Clinical Associate devotes both his time off the wards and a full 14 months of his 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the optional third year for Associates who have chosen nonclinical laboratories.

STAFF ASSOCIATES. Laboratories within the Heart, Lung, and Blood Institute sometimes have openings for Staff Associates appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Check List for the Institute. Selections for those positions are made by the Chief of the Laboratory. The position of Staff Associate is otherwise comparable to that of Research Associate.

CLINICAL ASSOCIATES IN SURGERY. The Surgery Branch of the National Heart, Lung, and Blood Institute appoints four to five Associates in Surgery for a 2-year period beginning each July 1. The program is primarily designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in a research or academic atmosphere. Candidates must have completed an internship and at least 1 year of surgical residence by the starting date of their appointment.

STAFF ASSOCIATE IN EPIDEMIOLOGY. The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood, and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental, and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or one of the field programs. The Associateships may begin after internship or after 1 year of training in a clinical residency or school of public health. Candidates interested in this possibility are encouraged to write Dr. Manning Feinleib, Chief, Epidemiology Branch, National Heart, Lung, and Blood Institute, Bethesda, Md. 20014, for more detailed information about specific assignments.

JOINT ENDOCRINOLOGY TRAINING PROGRAM. Clinical Associates from the National Heart, Lung, and Blood Institute may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to qualify associates for the Endocrinology Subspecialty Boards. National Heart, Lung, and Blood Institute participants will spend 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the Associate will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the Associate's 3 years will be spent primarily in research activity within the National Heart, Lung, and Blood Institute, although he will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two Associates to enter this program in any one year.

Formal Instructions

The major form of didactic postgraduate instruction is through the evening courses offered by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Research, Clinical, and Staff Associates are expected to take advantage of this academic work.

Laboratories Branches and Sections

The laboratories, branches, and sections of the National Heart, Lung, and Blood Institute, all of which are open to Clinical and Research Associates for their research work, are listed below with the names of their chiefs and a brief summary statement indicating the breadth of activities. Candidates desiring further information may obtain a current bibliography summarizing the activities of the current staff by writing to Dr. Jack Orloff, Director of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, Md. 20014.

SECTION OF PATHOLOGY (Head, Dr. William C. Roberts). This section is concerned with the study of morphologic aspects of cardiovascular disease and their correlation with functional derangements. Morphologic analyses include electron microscopy.

SECTION ON THEORETICAL BIOPHYSICS (Head, Dr. John L. Stephenson). The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned both with the formulation of theoretical models and with the development of mathematical and computational methods for their analysis. Currently much of the research in the section centers on the mechanism of urine formation in the mammalian kidney.

LABORATORY OF BIOCHEMICAL GENETICS (Chief, Dr. Marshall Nirenberg).

SECTION ON MOLECULAR BIOLOGY (Head, Dr. Marshall Nirenberg). This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, i.e., genetic programs for differentiation that determine informational reactions of neurons. Systems and problems involve the culture of mammalian cells and hybrid cells, and gene function for informational molecules such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

SECTION ON MACROMOLECULES (Head, Dr. Alan Peterkofsky). Studies of regulatory mechanisms involved in nucleic acid and protein biochemistry. Current emphasis is on regulation of cyclic AMP metabolism in microbial systems as well as mammalian protein synthesis.

LABORATORY OF BIOCHEMISTRY (Chief, Dr. Earl R. Stadtman).

SECTION ON ENZYMES (Head, Dr. Earl R. Stadtman). Studies of diverse enzyme systems that offer unique opportunities to elucidate a number of basic biochemical phenomena, namely, those concerned with vitamin-coenzyme function, the cellular regulation of metabolism, the energy-dependent transport of metabolites across membrane barriers, and mechanisms of enzyme action.

SECTION IN INTERMEDIARY METABOLISM AND BIOENERGETICS (Head, Dr. Thressa C. Stadtman). This section is concerned primarily with investigations on the mechanisms of anaerobic amino acid dissimilation and phosphorylation coupled with anaerobic electron transfer processes. Special emphasis is on the roles of various coenzymes (*viz*, vitamin B_{12} coenzyme, CoA, pyridoxal phosphate, flavins, pyridine nucleotides, lipoic acid, and naphthoquinones) and of various electron transfer proteins (*viz*, selenoproteins, ferridoxins, flavoproteins and sulfhydryl proteins) in these processes.

SECTION ON PROTEIN CHEMISTRY (Head, Dr. Ann Ginsburg). Studies on protein structure are directed toward understanding protein-ligand interactions, protein-protein interactions, and enzyme catalysis and regulation.

LABORATORY OF CELL BIOLOGY (Chief, Dr. Edward D. Korn). This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

SECTION ON CELLULAR BIOCHEMISTRY AND ULTRASTRUCTURE (Head, Dr. Edward D. Korn). This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the biochemistry of the plasma membrane in relation to endocytosis and the molecular and ultrastructural basis of cell motility. Cytoplasmic actin, moyosin, and related proteins are purified and their interactions studied and compared to their muscle counterparts. Opportunities are available for research and training in biochemistry and electron microscopy.

Section on Cellular Physiology (Acting Head, Dr. Evan Eisenberg). This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin and the troponins. Emphasis is on kinetic studies with pure proteins.

Section on Membrane Enzymology (Head, Dr. Richard Hendler). This section studies enzyme systems that require organization on or interaction with membranes in order to insure their proper functioning. The synthesis of DNA by enzyme complexes and the electron transport chain of *E. Coli* are presently being investigated.

Section on Organelle Biochemistry (Head, Dr. Martin Flavin). This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the physiological regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

Laboratory of Cellular Metabolism (Chief, Dr. Martha Vaughan). Major areas of research interest are: (1) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides in regulation of growth and metabolism of mammalian cells grown in culture; and (2) elucidation of the means through which certain hormones and humoral agents (e.g., insulin, prostaglandins, adrenal steroids, kinins, biogenic amines) affect the formation, degradation and/or action of cyclic nucleotides in several types of mammalian cells.

Laboratory of Chemical Pharmacology (Chief, Dr. James R. Gillette).

Section on Drug-enzyme Interaction (Head, Dr. James R. Gillette). This section studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objective has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

Section on Physiology (Head, Dr. Harriet M. Maling). This section studies interactions of drugs, particularly the mechanisms by which various treatments may alter the hepatotoxicity or pulmonary toxicity induced by various organic compounds. This includes study of how hepatotoxicity may be correlated with changes in the covalent binding of metabolites to liver lipids and proteins, changes in diene conjugation of microsomal lipids, and the formation of lipid peroxides, and effects on microsomal enzymes. The roles of endogenous mediators and autonomic and central nervous systems in the production of pulmonary edema and hindpaw inflammation are also under study.

Section on Clinical Pharmacology (Head, Dr. Jerry R. Mitchell). Research centers around the isolation and identification of drugs, drug metabolites, and endogenous substances (steroids, prostaglandins, monoamines) from biological fluids, and the study of their rates of formation and disposition (pharmacokinetics). Additional studies examine the oxidative mechanisms by which monooxygenases or superoxide anion convert chemically stable drugs to highly reactive imidoquinones, free radicals, and other toxic electrophiles. Possible cause-effect relationships are examined between these determinants and drug-induced tissue lesions (e.g., acetaminophen, phenacetin, furosemide, isoniazid, or methyldopa hepatic and renal injury), drug therapy (e.g., propranolol concentrations and hypertension control), or disease processes (e.g., pathogenetic role of various steroids in low-renin hypertension). Routine procedures include chemical synthesis of radioactive stable-isotope analogs (e.g., for quantitative mass fragmentography), and drug analysis by t.l.c., g.c., l.c., mass spectrometry, or radioimmunoassay.

SECTION ON DRUG-TISSUE INTERACTION (Head, Dr. Gopal Krishna). This section is involved in the study of the initial events occurring in cells as the result of a variety of drug (hormone)-cell interactions. This section has been studying the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, it has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

LABORATORY OF CHEMISTRY (Chief, Dr. Henry M. Fales). Conducts research into methods for the structural analysis of organic compounds specifically via mass spectrometry, X-ray crystallography, nuclear magnetic resonance, etc., in addition to classical methods of chemical degradation. Also studies biosynthetic pathways via tracer techniques and chemical synthesis.

SECTION ON PHYSIOLOGICAL CHEMISTRY (Head, Dr. John I. Pisano). Normal and pathologic states in man are studied at the molecular level by advanced analytical techniques. Under investigation are the prostaglandins and vasoactive peptides (e.g., bradykinin and angiotensin), precursor proteins of the peptides and the enzymes involved in their biosynthesis and degradation. Research is currently directed to the study of hypertension, coagulation, and fibrinolysis.

LABORATORY OF EXPERIMENTAL ATHEROSCLEROSIS (Chief, Dr. Donald L. Fry). The laboratory program is directed toward experimental evaluation of the pathological, physiological, biophysical, chemical, and histological processes involved in the genesis of atherosclerosis. These studies are carried out with tissues from both animal colonies and human subjects.

SECTION ON VASCULAR PHYSIOLOGY (Head, Dr. Donald L. Fry). Studies the relationship of physical-chemical and hemodynamic forces to the processes of transvascular transport of atherogenic precursor molecules into the vascular tissue space and the response of the cellular and structural elements of the wall to these forces and substances.

SECTION ON COMPARATIVE ATHEROSCLEROSIS AND ARTERIAL METABOLISM (Head, Dr. Robert W. Mahley). Studies the origin and fate of plasma lipoproteins in experimental animals and man in relationship to arterial wall metabolism and atherosclerosis. Primary emphasis is on lipid and protein chemistry, response of arterial cells grown in tissue culture, and comparative atherosclerosis.

LABORATORY OF KIDNEY AND ELECTROLYTE METABOLISM (Chief, Dr. Maurice B. Burg).

SECTION ON ELECTROLYTE TRANSPORT (Head, Dr. Jack Orloff).

SECTION ON RENAL MECHANISMS (Head, Dr. Maurice B. Burg).

SECTION ON MEMBRANE METABOLISM (Head, Dr. Joseph S. Handler). This section conducts research on the mechanism and regulation (hormonal and otherwise) of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, toad bladder, and erythrocytes. Electrophysiology and intermediary metabolism as related to transport are emphasized.

LABORATORY OF TECHNICAL DEVELOPMENT (Chief, Dr. Robert L. Bowman). Conducts research into instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicro methods to practical clinical instrumentation.

SECTION ON PULMONARY AND CARDIAC ASSIST DEVICES (Head, Dr. Theodor Kolobow). Conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This program includes the development of improved blood oxygenators, blood pumps, and control systems.

CARDIOLOGY BRANCH (Chief, Dr. Stephen E. Epstein).

SECTION ON CARDIOVASCULAR DIAGNOSIS (Head, Dr. David R. Redwood). Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by heart failure.

SECTION ON CARDIOVASCULAR PHARMACOLOGY (Head, Dr. Stephen E. Epstein). Current work is concerned with a comprehensive study of the terminal nervous innervation of the heart and how it influences electrical stability of the ventricle. Cellular effects of drugs are also under investigation in isolated cardiac tissue. The action of antiarrhythmic agents under conditions of myocardial ischemia is under investigation.

SECTION ON CLINICAL PHYSIOLOGY (Head, Dr. Stephen E. Epstein). Research objectives are aimed towards an understanding of the physiologic, anatomic, and biochemical mechanisms responsible for control of the normal heart and circulation, an elucidation of the alterations produced by ischemic and nonischemic heart disease, and an evaluation of interventions designed to reverse the biochemical and thereby the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic and echocardiographic (one- and two-dimensional systems) studies in man, electron microscopic and biochemical studies of tissues obtained from human surgical specimens as well as from the experimental animal, and pharmacologic investigations in man and animals.

SECTION ON MOLECULAR CARDIOLOGY (Head, Dr. Robert S. Adelstein). Current investigations are directed toward an understanding of the function and control of the contractile proteins of heart, blood platelets and other cells (both muscle and nonmuscle). Projects include: (a) the role of cyclic AMP and phosphorylation in the regulation of contractile protein function, (b) the characterization, on a molecular level, of the contractile proteins found in disease states such as asymmetric septal hypertrophy (ASH) and those characterized by congestive failure.

HYPERTENSION-ENDOCRINE BRANCH (Chief, Dr. Frederic C. Bartter). This branch represents a merger of the previous Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension, but its activities are wide-ranging, as indicated by the description of section activities.

SECTION ON STEROID AND MINERAL METABOLISM (Head, Dr. Frederic C. Bartter). The principal research of this section is directed towards the pathophysiology of hypertension. It is broadly approached through clinical, physiological, and biochemical studies on steroid metabolism, on the renin-angiotensin system, on the kallikrein-kinin system, on the sympathetic nervous system, including catecholamines, on prostaglandins, and on the interrelations of each of the above with mineral metabolism and the kidney. Other research of this section involves the functions of the adrenal glands, the parathyroid glands, the pituitary gland, and their interrelationships with the kidneys, studies on metabolic bone disease and metabolism and on the pathogenesis of nephrolithiasis, and studies on a wide variety of other endocrine disorders. There is strong emphasis on chronobiology and chronopharmacology.

SECTION ON EXPERIMENTAL THERAPEUTICS (Head, Dr. Harry R. Keiser). A wide spectrum of research opportunities is offered, ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins and cathecholamines conducted both in man and in experimental animals. Other current studies encompass disorders of serotonin and histamine.

SECTION ON BIOCHEMICAL PHARMACOLOGY (Head, Dr. Walter M. Lovenberg). This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of the enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is a prime objective, and investigations are extended from the molecular level to experimental animals and man.

MOLECULAR DISEASE BRANCH (Chief, Dr. Bryan Brewer). The activities of this branch are concerned primarily with the metabolism and transport of lipids. This includes the structure and relationships of lipoproteins and their apoprotein constituents, and the nature of enzymes involved in fat metabolism and the regulations of their activities, particularly as they control the concentrations of lipids in plasma and tissues. A major interest is dyslipoproteinemia and other metabolic diseases, especially those which are genetically determined, and related to lipid transport, metabolism and to atherosclerosis. The activities of the sections are integrated in such a way that, if they wish, associates may participate in collaborative work involving several sections.

SECTION ON PEPTIDE CHEMISTRY (Head, Dr. H. Bryan Brewer). Research is directed toward the analysis and synthesis of polypeptide hormones and lipoproteins with the object of developing knowledge of structure-function relationships.

SECTION ON LIPOPROTEIN STRUCTURE AND FUNCTIONS (Head, Dr. Peter Herbert). Research is concerned with isolation, identification, and structure of apolipoproteins, and elucidation of their special functions and interrelationships.

MOLECULAR HEMATOLOGY BRANCH (Chief, Dr. W. French Anderson). This branch is concerned with investigations into the mechanism and regulation of mammalian gene expression and protein synthesis, specifically relating to hemoglobin and to diseases involving the regulation of hemoglobin synthesis.

SECTION ON MOLECULAR GENETICS (Head, Dr. W. French Anderson). This section conducts investigations into the mechanism and regulation of hemoglobin biosynthesis. Studies include cell-free hemoglobin synthesis directed by isolated mRNA, purification and characterization of mammalian initiation and elongation factors, globin mRNA transcription from bone-marrow chromatin, and attempts to synthesize a DNA gene coding for globin mRNA with the use of the enzyme reverse transcriptase.

SECTION ON CLINICAL HEMATOLOGY (Head, Dr. Arthur W. Nienhuis). Application of the techniques of cell and molecular biology aimed at the understanding and treatment of human disorders of hemoglobin synthesis and erythroid differentiation. Major research areas include: the regulation of specific globin gene synthesis in differentiating erythroid cells *in vitro* and expression of globin genes in somatic cell hybrids. Patients with a broad range of red blood cell diseases are studied on the clinical service. Intracellular factors which influence the binding of oxygen to hemoglobin are being explored, particularly as they pertain to the deoxygenation and intracellular gelation of sickle hemoglobin. The value of iron chelation therapy in patients with transfusional hemosiderosis is under investigation.

PULMONARY BRANCH (Chief, Dr. Ronald G. Crystal).Research in this branch is designed to approach the structure and function of respiratory tissue through molecular biology. Both laboratory and clinical investigations are conducted.

SECTION ON PULMONARY BIOCHEMISTRY (Head, Dr. Ronald Crystal). Investigation of the molecular basis of lung function in health and disease using techniques of molecular biology and tissue culture with specific emphasis on the regulation of synthesis and degradation of connective tissue elements. Clinical research is directed toward correlating physiologic, biochemical, and morphologic observations in patients with interstitial lung disease and patients with hereditary disorders of connective tissue.

SECTION ON MOLECULAR PHARMACOLOGY (Head, Dr. Elwood O. Titus). Studies the mechanisms by which neurohumoral transmitters, hormones, and drugs affect pulmonary and cardiovascular function. Activities include the characterization of cellular receptors for drugs and hormones, studies of the metabolism of biogenic amines in lung, and studies of the ionic mechanisms underlying signal transmission from nerve to muscle. Considerable emphasis is placed on the use of physical methods such as optical rotatory dispersion, fluorescence, nuclear magnetic resonance and electron spin resonance for the study of drug protein interactions.

SURGERY BRANCH (Chief, Dr. Andrew G. Morrow).

National Institute of Allergy and Infectious Diseases

Scientific Director
Sheldon M. Wolff, M.D., F.A.C.P., Clinical Director

The NIAID annually appoints Associates for the laboratories described below. Clinical Associates are selected by the Clinical Director, and appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Research Associate appointments in the other laboratories may begin after internship or residency training. In general, those appointments which begin after 1 or more years of residency training have some degree of responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Appointees through the Early Commissioning Program will be regarded as appointees through other programs, and final identification as to positions for which they are being considered and as to whether or not the position will afford 1 or more years of residency training before entry will be made to prospective candidates at the time of interview.

Specific answers to any questions or additional information may be obtained by applicants from Scientific Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. 20014. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests of applicant and information desired.

The LABORATORY OF CLINICAL INVESTIGATION (Sheldon M. Wolff, M.D., Chief).

The National Institute of Allergy and Infectious Diseases appoints six to eight Clinical Associates. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned clinical responsibilities are made during the second or third year except as dictated by the needs of the Clinical Associates' research.

There are 52 research beds. Clinical Associates consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each Clinical Associate selects his own area of investigative interest under the general preceptorship of the Clinical Director and the senior members of the staff of the Laboratory of Clinical Investigation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the Clinical Associate works, the subspecialty boards in infectious diseases or allergy will usually credit the training received towards admission to these board examinations.

Opportunities exist for research in a wide variety of areas of infectious and immunological disease. Examples of studies now in progress are:

- The etiology and pathogenesis of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- Pathogenesis of both experimental and clinical fevers.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The pathogenic mechanisms of the aspirin sensitivity-asthma syndromes.
- The structure and function of immunoglobulins of human and lower animal origin.
- The application of electron microscopy, autoradiographic, and cytochemical techniques to studies of cellular interactions in immunologic information processing both in humoral and cellular events.
- The interrelationship of coagulation and fibrinolysis to kinin generation and the role of these enzymatic pathways in the pathogenesis of reactions of the immediate hypersensitivity type.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Study of chronic bacterial pulmonary infections.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Dr. Sheldon M. Wolff.

Research Areas and Senior Staff

Allergic Diseases—Allen P. Kaplan, M.D., Michael A. Kaliner, M.D.
  Bacterial Diseases—Herbert Y. Reynolds, M.D.
  Biologic Structure—Alan S. Rosenthal, M.D.
  Clinical Allergy and Hypersensitivity—Charles H. Kirkpatrick, M.D.
  Clinical Immunology—Michael M. Frank, M.D.
  Clinical Mycology—John E. Bennett, M.D., Kyung J. Kwon-Chung, Ph.D.
  Clinical Parasitology—Franklin A. Neva, M.D., Eric A. Ottesen, M.D.
  Clinical Physiology—Anthony S. Fauci, M.D., John I. Gallin, M.D., Charles A. Dinarello, M.D.
  Medical Virology—Raphael Dolin, M.D.

The LABORATORY OF VIRAL DISEASES (Wallace P. Rowe, M.D., Chief) conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses, and on host antiviral defense mechanisms.

Studies of tumor viruses are concentrated on murine leukemia viruses, adenovirus-SV40 hybrid viruses, and human papoviruses. These studies include investigations of the interactions between defective and competent viruses, the natural history and epidemiology of tumor viruses, genetic transmission of leukemia viruses in mice, and the viral and host genetic factors of importance in viral tumorigenesis.

The mechanism of action of interferon and inducers of interferon is studied by biological and biochemical approaches; the development and evaluation of new interferon inducers for possible clinical application are also undertaken.

Other areas of study are the biology of parvoviruses and the recently discovered viruses of certain medically important protozoa.

Research Areas and Senior Staff
  Cellular Virology—Kenneth K. Takemoto, Ph.D.
  Molecular Virology—Hilton B. Levy, Ph.D.
  Viral Oncology—Wallace P. Rowe, M.D.

The LABORATORY OF BIOLOGY OF VIRUSES (Norman P. Salzman, Ph.D., Chief) is primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain specific antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for associates is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff

Biochemical Virology—Norman P. Salzman, Ph.D.
Macromolecular Biology—Bernard Moss, M.D., Ph.D.
Molecular Structure—James A. Rose, M.D.
Physical Biochemistry—Malcolm A. Martin, M.D.

The LABORATORY OF INFECTIOUS DISEASES (Robert M. Chanock, M.D., Chief) is concerned with the basic behavior of viral and mycoplasmal pathogens which play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as cornaviruses and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycoplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff

Epidemiology—Albert Z. Kapikian, M.D.
Hepatitis Virus—Robert H. Purcell, M.D.
Mycoplasma—Joseph G. Tully, Ph.D.
Respiratory Viruses—Robert M. Chanock, M.D.

The LABORATORY OF IMMUNOLOGY (William E. Paul, M.D., Chief) is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in both the prevention and pathogenesis of human diseases.

Areas of active investigation now include the study of the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells.

Further, active studies of the role of different lymphocyte classes in a variety of human diseases are underway, and models for the study of the role of cellular immune responses in tumor immunity and for the investigation of immunotherapy of tumors are being developed.

Associates will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff

Cellular Immunity—Ira Green, M.D.; Ethan M. Shevach, M.D.
Immunology—Donald E. Mosier, M.D., Ph.D.; William E. Paul, M.D.
Immunochemistry—John K. Inman, Ph.D.
Immunogenetics—Rose G. Mage, Ph.D.; Rose Lieberman
Molecular Structure—Myron J. Waxdal, Ph.D.

The LABORATORY OF MICROBIAL IMMUNITY (Richard Asofsky, M.D., Chief) is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunological methods, offer the associate comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution, and susceptibility of the interacting components to various treatments which suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations. Autoimmune phenomena are studied using immune complex nephritis as a model. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The relationship of this disease to the presence and activity of such integrated viruses as the murine leukemia agents are studied. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff

Biochemistry—Benjamin Prescott, Ph.D.
Experimental Pathology—Richard Asofsky, M.D.
Microbiology and Immunology—Phillip J. Baker, Ph.D.

The Laboratory of Parasitic Diseases (Franklin A. Neva, M.D., Chief) is engaged in both basic and applied studies of parasitic diseases of man. Basic research is conducted with a variety of parasites such as leishmania, trypansomes, malaria, amebae, toxoplasma, schistosomes, filaria, and tapeworms. Current studies include comparative mechanisms of energy transfer, non-heme iron respiratory proteins, ultrastructure of parasites, and *in vitro* host-parasite interactions at the cellular level utilizing specialized optical techniques. Increasing emphasis is being devoted to consideration of immunologic response of the host in parasitic infections, both humoral and cellular. Some experimental infections of animals, such as malaria, leishmaniasis, and filariasis are utilized as models of naturally occurring disease in man. Availability of different species of simian parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate circumstances permit, certain problems are studied in the field in collaboration with local institutions. A Section of Clinical Parasitology is maintained within the Laboratory of Clinical Investigation providing a mutually useful opportunity for clinical studies.

The Pacific Research Section in Hawaii (under the direction of Dr. Leon Rosen) conducts research on vector-borne viral diseases as well as certain parasitic and other diseases of particular importance to the Pacific area. The isolated ecologic environment of the Pacific Islands is utilized for epidemiologic investigations. Current work is mainly on dengue hemorrhagic fever, swine influenza, and venereal diseases.

Within reasonable limits and with guidance of senior staff, associates can select their area of work and a preceptor. In addition, an organized program provides associates a broad exposure to medical parasitology including clinical aspects.

Research Areas and Senior Staff

Cell Biology and Immunology—Harley G. Sheffield, Ph.D.
Host-Parasite Relations—Allen W. Cheever, M.D.
Malaria—Louis H. Miller, M.D.
Parasitic and Vector-borne Viral Diseases, Pacific Area—Leon Rosen, M.D.
Parasite Growth and Differentiation—Louis S. Diamond, Ph.D.
Physiology and Biochemistry Section—Eugene C. Weinbach, Ph.D.

The Laboratory of Streptococcal Diseases (Roger M. Cole, Ph.D., M.D., Chief) investigates the genetics of streptococci and their bacteriophages, particularly in relation to ultrastructure, cell wall and surface composition, antigenic structure, competence, and autolytic enzymes. Current studies utilize phage-mediated transduction in group A streptococci; and transduction, DNA-mediated transformation and transfection, and lysogenization in group H streptococci. Efforts are directed to genetic transfer of natural characteristics (i.e., other than antibiotic resistance) which may alter epidemiological patterns in human disease. Emphasis is on surface antigens which can, if changed, result in differences in virulence, immunogenicity, phage susceptibility, adherence, and serologic recognition.

Other studies include virus-host reactions of newly-discovered viruses (phages) of some mycoplasmas; host-parasite interactions of gonococci; and the nature and role of cell wall and membrane components of staphylococci.

Associates have opportunities for training and experience in electron microscopy, microbial genetics, phage virology, and appropriate bacteriologic and biochemical methods related to the above or similar areas of investigation.

Research Areas and Senior Staff

Streptococci and Bacteriophages—Roger M. Cole, Ph.D., M.D.
Microbial Genetics—Jon M. Ranhand, Ph.D.
Microbial Composition and Function—Eskin Huff, Ph.D.; Theodore S. Theodore, Ph.D.
Microbial Ultrastructure—Roger M. Cole, Ph.D., M.D.

The ROCKY MOUNTAIN LABORATORY (Herbert G. Stoenner, D.V.M., Director) located at Hamilton, Mont., is internationally recognized for research on rickettsial and tick-borne diseases. The laboratory is a WHO Reference Center for Human Rickettsioses. In medical entomology and acarology, principal projects include biology and systematics of ticks and mites, ecology of selected tick- and mosquito-borne viruses, and general and subcellular relationships between arthropod-borne microbiota and their vectors as studied by various approaches, including arthropod tissue culture and electron microscopy.

Various aspects, particularly immunology and microbiology, of selected infectious diseases are under investigation. Scrapie and progressive pneumonia of sheep, and Aleutian disease and encephalopathy of mink are studied as models of chronic degenerative diseases of man. Limited studies are made on pertussis, rabies, tularemia, and the PTL group of organisms. More basic inquiries are made into fundamental mechanisms in delayed hypersensitive, cell-mediated immunity, and antibody production according to immunoglobulin class.

The fractionation of microbial agents, such as *Mycobacteria*, *Bordetella*, and Gram-negative organisms, by special biophysical and biochemical methods and the role of these subcellular fractions in immunity, hypersensitivity, tumor immunology, and other host responses are subjects of major investigations.

Opportunities for training associated with these research projects are provided in comparative pathology, electron microscopy, scanning electron microscopy, virology, immunology, immunochemistry, and a wide variety of specialized biophysical and biochemical methodology.

Research Areas and Senior Staff

Allergy and Immunology—John J. Munoz, Ph.D.
Slow Viral Diseases—William J. Hadlow, D.V.M.
Epidemiology—Robert N. Philip, M.D.
Medical Zoology and Zoonotic Diseases—J. Frederick Bell, M.D.
Molecular Biology—Edgar E. Ribi, Ph.D.
Rickettsial Diseases—Willy Burgdorfer, Ph.D.

National Institute of Arthritis, Metabolism and Digestive Diseases

J. E. Rall, M.D., Ph.D., Director of Intramural Research
John L. Decker, M.D., Clinical Director

Clinical Associates

The NIAMDD recruits about 10 new Clinical Associates each year. The assignments are for 2 or 3 years and usually are not extended.

Each Clinical Associate is assigned to one of the clinical branches or sections, within which he carries out both clinical work and laboratory studies. He is, in effect, an apprentice clinical investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The associate is encouraged to choose his own problem for independent investigation, subject to the limitation that the facilities required for its successful pursuit and the technical advice and supervision necessary must be available to the branch or section in which he is working. In addition, he provides professional care for the research patients admitted to the service of his branch chief and assists in the work of that branch in the outpatient department. There is considerable variation among the branches of NIAMDD with respect to the proportion of the associate's time required for patient care activities.

Clinical Associates of the Clinical Endocrinology, Diabetes, and Metabolic Diseases branches participate in a 3-year Inter-Institute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIAMDD Clinical Associates may also spend a third year in the Endocrinology Program.

Vacancies do not necessarily occur within each program area each year; the Program Area Selection check List indicates the vacancies to be filled at any one time. The chiefs of branches or sections with openings and the Clinical Director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm his acceptance of the position to which he was assigned.

The Clinical Research Branches are listed below with the names of the premanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Dr. John L. Decker, Clinical Director, NIAMDD, Building 10, Room 9N222, NIH, Bethesda, Maryland 20014. Supplementary information sheets on each branch, together with selected bibliographic citations, are available on request.

Staff Associate in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment studying the epidemiology of chronic disease (diabetes, arthritis, cholelithiasis, etc.) among the Pima Indians of Arizona. In addition, clinical research opportunities are available in the Clinical Research Center of the Phoenix Indian Hospital. These Associateships begin after internship. Candidates interested in this possibility are encouraged to write Dr. Peter H. Bennett, Epidemiology & Field Studies Branch, NIAMDD, 1440 E. Indian School Road, Phoenix, Ariz. 85014, for more detailed information.

Research Associates

NIAMDD has four positions available each year for Research Associates. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During his stay here, each Research Associate will devote the larger part of his time to participation in laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should he elect a clinical area, he would not participate in clinical care of patients. The Research Associate, approximately 1 year prior to beginning, will visit NIAMDD to select the laboratory and preceptor with whom he wishes to work. Candidates desiring further information about the laboratories, staff and bibliography can obtain this by writing Dr. J. E. Rall, Director of Intramural Research, NIAMDD, National Institutes of Health, Bethesda, Md. 20014.

Clinical Research Branches

Arthritis and Rheumatism Branch—Dr. John L. Decker

Section on Connective Tissue Disease—Drs. John L. Decker, John H. Kilippel, Paul Plotz, and Alfred D. Steinberg

The pathogenesis of systemic lupus erythematosus (human and mouse models) is under study. Suppressor and activator lymphoclyte isolation, development of stable immune complexes, and studies of anti-viral agents in the mouse model are in progress. Clinical work is on cytotoxic drugs in lupus nephritis, on survivorship variations with disease pattern, and on aspects of drug effects upon patients with lupus or rheumatoid arthritis.

Section on Chemical Immunology—(Dr. Henry Metzger).

The section is involved in fundamental research on the structure and mechanism of immunoglobulins and their receptors on cells. Methods used include protein chemistry, immunochemistry, tissue culture, electronmicroscopy, and others.

Section on Human Biochemical Genetics—Drs. Elizabeth F. Neufeld and Raphael D. Camerini-Otero

Studies of a group of human genetic diseases cover basic aspects (e.g., research on those enzymes and mechanisms which are altered by the mutations) and practical applications (diagnosis and carrier detection, preparation of enzymes for replacement trials).

CLINICAL ENDOCRINOLOGY BRANCH—Drs. Jacob Robbins, Jan Wolff, Saul Rosen, Harold Edelhoch, and Bruce Weintraub

Activities range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid and polypeptide hormones. Laboratory research includes fundamental and applied protein chemistry, hormone actions, cellular control mechanisms.

CLINICAL HEMATOLOGY BRANCH—Dr. N. Raphael Shulman

Laboratory work concerns the biochemistry of blood coagulation, platelet physiology and metabolism, and various problems in the field of immunohematology. Examples of current work are: isolation and characterization of Factor VIII and platelet aggregating factor, studies of the mechanism of action of circulating anticoagulants, evaluation of platelet nucleotide metabolism with respect to platelet function, and analysis of molecular changes in prothrombin during its conversion to thrombin. Clinical work involves patients with hemorrhagic and immunologic disorders relevant to the laboratory studies.

DIABETES BRANCH—Drs. Jesse Roth, Phillip Gorden, Ronald Kahn, and Matthew Rechler

Attention is on peptide hormones, especially insulin, growth hormone, and insulinlike growth factors. Recent work has been largely on the interaction of the peptide hormones with their receptors on the surface membrane of target cells, with emphasis on situations where the concentration or affinity of the receptor changes in response to intracellular or extracellular events. A broad range of experimental approaches are used to explore these processes including cell culture, purification of hormones and of membrane components, and studies of rodents and people with a wide variety of insulin resistant conditions.

DIGESTIVE DISEASES BRANCH

SECTION ON GASTROENTEROLOGY—Drs. Jerry D. Gardner and Denis M. McCarthy

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunological processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology biochemistry and immunology.

SECTION ON DISEASES OF THE LIVER—Drs. Paul D. Berk and E. Anthony Jones

Hepatic transport processes are investigated by means of kinetic studies in patients, in animals, in isolated perfused livers, and subcellular preparations. Investigations of various approaches to the design of an artificial liver are actively pursued. Studies of cellular immunology are applied to the investigation of chronic hepatitis and primary biliary cirrhosis, and metabolic investigations are conducted in patients with disorders of copper and protein metabolism. Emphasis is on the application of basic biochemical, biophysical, immunologic and mathematic techniques to clinical investigation.

METABOLIC DISEASES BRANCH—Drs. Gerald D. Aurbach and Stephen Marx

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone and calcitonin. The clinical program involves studies of patients with disorders of mineral metabolism. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is available for *in vitro* studies and is cryopreserved for a study of management of postoperative hypoparathyroidism with parathyroid autotransplantation.

PEDIATRIC METABOLISM BRANCH—Dr. Paul A. diSant'Agnese

Cystic fibrosis of the pancreas is the target of both laboratory and clinical work. Glycoproteins, polyamines, the circulating "cystic fibrosis" factor and other substances are analyzed for their possible relationship to the sweat and saliva electrolyte abnormalities. Techniques used include amino acid analyses, automated ion exchange and thin-layer chromatography, radioisotope analyses by liquid scintillation counting and tissue culture. A variety of clinical aspects such as Vitamin E deficiency, the reninaldosterone axis, cyclic nucleotides and the like are studied as the course and complications are documented.

PHOENIX CLINICAL RESEARCH UNIT—Dr. Peter H. Bennett

Diseases unique to or particularly prevalent among American Indians are studied. Current investigations focus on diabetes, gallbladder disease and lipid disorders and include studies of insulin receptors, hormonal abnormalities in diabetic and prediabetic subjects, lipid and lipoprotein metabolism, and studies of biliary lipid metabolism and physiology in Southwestern American Indians. Investigations are carried out at the Phoenix Clinical Research Center, a 24-bed clinical research unit with full supporting laboratory facilities located within the Indian Health Service Referral Hospital in Phoenix, Arizona.

Basic Research Laboratories

MATHEMATICAL RESEARCH BRANCH—Dr. John Z. Hearon

LABORATORY OF NUTRITION AND ENDOCRINOLOGY—Dr. Martin Rodbell
- Section on Nutritional Biochemistry—Dr. John G. Bieri
- Section on Endocrinology—Dr. Robert O. Scow
- Section on Vitamin Metabolism—Dr. Bernard Kaufman
- Section on Developmental Biochemistry—Dr. Robert T. Simpson
- Section on Membrane Regulation—Dr. Martin Rodbell

LABORATORY OF BIOCHEMISTRY AND METABOLISM—Dr. G. Gilbert Aswell
- Section on Enzymes and Cellular Biochemistry—Dr. William B. Jakoby
- Section on Intermediary Metabolism—Dr. Yale J. Topper

LABORATORY OF EXPERIMENTAL PATHOLOGY
  Section on Histochemistry—Dr. George G. Glenner
  Section on Chemical Pathology—Dr. Robert Friedman
  Section on Biophysical Histology—Dr. Ned Feder
  Section on Cytogenics—Dr. J. H. Tjio

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Dr. Herbert Tabor
  Section on Pharmacology—Dr. Herbert Tabor
  Section on Biochemistry—Dr. Victor Ginsburg
  Section on Biochemistry of Amino Acids—Dr. Simon Black
  Section on Biochemistry of Cell Regulation—Dr. Leonard Kohn

LABORATORY OF CHEMISTRY—Dr. Bernhard Witkop
  Section on Carbohydrates—Dr. C. Glaudemans
  Section on Medicinal Chemistry—Dr. Everette L. May
  Section on Biochemical Mechanisms—Dr. Louis A. Cohen
  Section on Metabolites—Dr. Bernhard Witkop
  Section on Microanalytical Services and Instrumentation—Dr. David Johnson
  Section on Pharmacodynamics—Dr. John W. Daly

LABORATORY OF PHYSICAL BIOLOGY—Dr. Richard J. Podolsky
  Section on Comparative Physiology—Dr. John B. Buck
  Section on Cellular Physics—Dr. Richard J. Podolsky

LABORATORY OF CHEMICAL PHYSICS—Dr. Edwin D. Becker
  Section on Molecular Biophysics—Dr. Edwin D. Becker
  Section on Physiology—Dr. Paul Altland
  Section on Spectroscopy and Structure—Dr. Elliot Charney
  Section on Membrane Biophysics—Dr. William A. Hagins

LABORATORY OF MOLECULAR BIOLOGY—Dr. Gary Felsenfeld
  Section on Metabolic Enzymes—Dr. Martin Gellert
  Section on Molecular Genetics—Dr. Jun-ichi Tomizawa
  Section on Physical Chemistry—Dr. Gary Felsenfeld
  Section on Molecular Structure—Dr. David R. Davies
  Section on Microbial Genetics—Dr. Robert Martin
  Section on Organic Chemistry—Dr. H. Todd Miles
  Section on Theoretical Molecular Biology—Dr. Terrell Hill

LABORATORY OF CHEMICAL BIOLOGY—Dr. Christian B. Anfinsen
  Section on Protein Chemistry—Dr. Christian B. Anfinsen
  Section on Macromolecular Biology—Dr. Alan Schecter
  Section on Protein Conformation—Dr. Hiroshi Taniuchi

LABORATORY OF BIOPHYSICAL CHEMISTRY—Dr. Koloman Laki
  Section on Bioenergetics
  Section on Macromolecules—Dr. Harry A. Saroff
  Section on Physical Biochemistry—Dr. Koloman Laki

National Institute on Aging

Intramural Research Program

Nathan W. Shock, Ph.D., Acting Scientific Director
Reubin Andres, M.D., Acting Clinical Director

The Intramural Research Program of the National Institute on Aging is located at the Gerontology Research Center in Baltimore, Md.

The multidisciplinary program of the Center, located in a special research building on the campus of the Baltimore City Hospital, offers 2-year Clinical (primarily clinical research) and Staff (primarily basic research) Associate training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, associates may participate in clinical activities of the Baltimore City Hospital and the nearby Johns Hopkins Hospital.

In addition to the 2-year appointments, a 3-year program of clinical and research training in collaboration with the Division of Cardiology, Department of Medicine, Johns Hopkins University, the Department of Psychiatry, Johns Hopkins University, or the Department of Medicine, Baltimore City Hospital, is offered to a limited number of candidates. Under this program, the associate spends his first year in clinical training as a Resident Physician or Clinical Fellow in one of the above departments. The second and third years are spent in clinical or laboratory research on gerontology or geriatrics at the Center.

Associates participate in a seminar conducted by the staff of the Center which presents a comprehensive view of research in aging. Weekly research conferences are presented by members of the staff and invited lecturers.

In support of the programs the Center maintains extensive animal colonies to provide rats, mice, and house flies of known ages, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment. Computer facilities for electronic data processing are available at the Center. Instruction in the use of computers in laboratory research is provided. The library of the Center includes standard scientific journals as well as an extensive collection of the literature on aging research. The Center also has approved clinical research programs in which 650 male volunteers, aged 18–96,report to the Center regularly at 1–2 year intervals for 2 1/2 days of intensive testing.

The Gerontology Research Center is composed of four branches:

LABORATORY OF CELLULAR AND COMPARATIVE PHYSIOLOGY (Takashi Makinodan, Ph.D., Chief). This laboratory is concerned with the effects of age on cellular differentiation in humans and other mammalian species. Currently, emphasis is placed on immunologic, biochemical, and genetic evaluations of cells of normal and genetically altered tissues.

Research in immunology (Takashi Makinodan, Ph.D., Albert A. Nordin, Ph.D., and William H. Adler, M.D., Program Coordinators) is focused on the nature, cause(s) and mechanism(s) of the decline with age in normal cell-mediated and humoral immune functions. Research has also been initiated for ways of replenishing the defective immune system in aged animals. Research in human immunology has also been initiated (Marguerite M. B. Kay, M.D., Program Coordinator) with focus on immunologic activities of circulating cells.

Research in mammalian cell biology (Edward L. Schneider, M.D., Program Coordinator) is focused on studies of cell replication, repair of DNA damage, and nucleic acid metabolism in both human cells in culture and in living animal tissues. The effect of parental age on the production of genetically abnormal offspring is being examined in appropriate animal models.

The laboratory also operates a high resolution electron microscopy laboratory (transmission and scanning) with emphasis on changes in cell membrane receptors with age (M. M. B. Kay, M.D.).

CLINICAL PHYSIOLOGY BRANCH (Reubin Andres, M.D., Chief). This branch is primarily concerned with studies on physiological changes occurring during the entire adult age span. Studies include quantitation of age changes, elucidation of mechanisms underlying these changes, and the relation between aging processes and specific disease states.

The ENDOCRINOLOGY SECTION (Robert I. Gregerman, M.D., Chief) conducts studies on (a) the molecular bases of age-related changes of hormone responses, especially as related to the biochemistry of the adenylate cyclase system and hormone receptors, (b) aging and the endocrinology of the reproductive system, and (c) the enzymology and peptide chemistry of the renin-angiotensin system.

The CARDIOVASCULAR SECTION (Edward G. Lakatta, M.D., Chief) investigates cardiovascular hemodynamic function in man using noninvasive methods and in the rat and dog by a variety of experimental techniques. Studies on the effects of age on the biophysical properties of cardiac muscle are also conducted in animal models.

The METABOLISM SECTION (Reubin Andres, M.D., Chief) conducts research on the kinetics of glucose homeostasis and its endocrine control. Factors controlling insulin secretion, including gastrointestinal insulinotrotropic hormone, are quantified using the servo-control gulcose clamp technique in man. Efforts are directed at the evaluation of normal physiology and changes with aging, obesity, diabetes, and other metabolic disorders.

The HUMAN PERFORMANCE SECTION (Arthur H. Norris, M.A., Chief). This section is responsible for a wide variety of studies on age changes in body composition, pulmonary and exercise physiology, and neuromuscular function.

LABORATORY OF BEHAVIORAL SCIENCES (Bernard T. Engel, Ph.D., Chief). This program includes studies of the effects of aging on motor behavior, perceptual skills, learning, memory, problem-solving ability, and personality characteristics. There are also studies on the interrelationships among aging and autonomic responses. The clinical applications of voluntary autonomic control are being investigated. Laboratory facilities exist for measuring cognitive and perceptual functions in man; psychophysiological responses in man; learning and motor behavior in rodents (including selected inbred strains of mice); learning, cardiovascular and neuropsychological responses in monkeys.

The LABORATORY OF MOLECULAR AGING (Bertram Sacktor, Ph.D., Chief) investigates mechanisms of the control of metabolism and of the expression of genetic information. The thrust of the research on metabolic processes is directed toward membrane biology. The problems and questions studied relate to: (1) the molecular organization of the membrane; (2) the role of the membrane in vectoral transport of small molecular species and proton-motive force; (3) the membranal reception of hormonal stimuli, the transduction and propagation of these stimuli; (4) the catalytic and integrative function of membranes; (5) the turnover of membranes; and (6) the failure to maintain membrane structure, leading to cell death. The thrust of the work on the propagation of genetic information is directed toward the interaction of metal ions with nucleic acids and proteins with the object of understanding these interactions in terms of biological function and particularly in the replication of DNA, transcription of RNA, and the synthesis of proteins.

National Institute of Child Health and Human Development

Intramural Research Program

James B. Sidbury, M.D., Scientific Director
Ronald Chez, M.D., Acting Clinical Director

The NICHD has 6-8 associate positions available each year. The appointments are for two or three years. The specific programs are indicated below. More detailed description of specific programs is available on request.

The Reproductive Research program is approved for accreditation by the Endocrinology Boards. The Pregnancy Research Branch has a research program correlating the study of model systems with investigations of high risk pregnancies in patients. The pediatric component of the perinatal program includes developmental pharmacology, neonatology, and biochemical genetics. A new pediatric program is being established. The trainee who selects the pediatric program will rotate on the infant and children's wards, participating in clinical research programs as well as providing the care on those wards. During the first year he will select the laboratory he wishes to work in for the subsequent two years. This permits the trainee to select the laboratory experience after more knowledgeable exposure. Completion of the PL-2 pediatric experience is required.

The BEHAVIORAL BIOLOGY BRANCH (Phillip G. Nelson, M.D., Ph.D., Chief) conducts electrophysiologic and biochemical studies of the neurobiologic basis for short- and long-term interaction between nerve cells. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques. Combined molecular and behavior methods are used in the analysis of experiential modification of brain function.

The SECTION ON BRAIN AND BEHAVIOR (David Symmes, Ph.D., Head). Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed using microelectrode computer techniques. Behavioral consequences of brain lesions are studied.

The SECTION ON FUNCTIONAL NEUROCHEMISTRY (Harold Gainer, Ph.D., Head), conducts analysis of biochemical changes in identified neurons associated with electrophysiological and behavioral alterations. Specific neuronal protein synthesis and axoplasmic transport, glial-neuronal interactions, pacemaker activity, and neural peptides are studied.

The SECTION ON NEUROBIOLOGY (Phillip G. Nelson, M.D., Ph.D., Head). Tissue cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied electrophysiologically and biochemically. Long-term interactions between neurons and between nerve and muscle are of particular interest.

The LABORATORY OF BIOMEDICAL SCIENCES (J. C. Robinson, M.D., Ph.D., Chief) conducts basic research in developmental enzymology, intermediary metabolism, and physiological controls.

The SECTION ON DEVELOPMENTAL ENZYMOLOGY (J. C. Robinson, M.D., Ph.D., Chief). Primary interest centers on the identification and characterization of pregnancy-associated maternal blood plasma enzymes and proteins, the characterization of enzymes synthesized by the placenta, and an analysis of some of the factors involved in enzyme induction in the developing fetus.

The SECTION ON PHYSIOLOGICAL CONTROLS (Walter H. Glinsmann, M.D., Chief) is concerned with hormonal, neurotransmitter, and substrate regulation of cell function and biochemical differentiation. Current studies focus on phosphoproteins controlling hepatic glucose output, substrate- and hormone-dependent induction of enzymes in embryonic and adult liver, mode of action of biogenic amines, and neuroendocrine regulation of indole metabolism in the pineal gland.

SECTION ON INTERMEDIARY METABOLISM (Gordon Guroff, Ph.D., Chief). This Section is involved in studies on the mechanism of action of enzymes of neurochemical interest, the biosynthesis and degradation of macromolecules in neural tissue, and the mechanism of action of nerve growth factor. Other studies concern the development of animal analogs of mental retardation through the use of specific chemical agents and enzyme inhibitors, the investigation of screening procedures for enzyme defects in mental retardation, and the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation. The overall efforts of the Section are to understand how changes in specific enzymes or growth factors lead to changes in the biochemical and behavioral patterns of the whole animal.

LABORATORY OF MOLECULAR GENETICS (Philip Leder, M.D., Chief) is concerned with the transfer and expression of genetic information. A wide variety of regulated biologic systems is under investigation, including models chosen from the areas of developmental biology, virology, cellular immunology, bacterial physiology, and bacteriophage genetics. At the present time, particular attention is being given to molecular aspects of the haematopoietic system, development of immunocompetency in cultured cells, differentiation of the embryonic chick lens, expression of the SV40 and adenovirus genomes, and structural and physiologic aspects of certain RNA tumor viruses. In addition, studies in prokaryocytes are concerned with the mechanism and control of protein and RNA synthesis and with the replication and recombination of the bacteriophage lambda.

Perinatal Biology Program consists of the Developmental Pharmacology Branch, Pregnancy Research Branch, and Neonatology Branch.

The Developmental Pharmacology Branch (Daniel W. Nebert, M.D., Chief) investigates the molecular mechanisms underlying genetic differences and environmental factors influencing drug metabolism in man. This program complements and supports the ongoing Institute program in Perinatal Biology.

The Section on Pharmacogenetics and Molecular Teratology (Daniel W. Nebert, M.D., Head). The primary interest centers around the development of methods *in vitro* and in cell culture for assessing and predicting teratogenic, mutagenic, or carcinogenic effects of exogenous or endogenous inducing compounds in animal model systems and in man. Developmental curves of drug-metabolizing enzymes and the transplacental inducing effect of drugs and environmental contaminants are investigated as possibly important factors in the etiology of birth defects.

The Section on Molecular Toxicology (Snorri S. Thorgeirsson, M.D., Ph.D., Head) conducts research on the mechanisms of toxicity and carcinogenicity caused by drugs and environmental chemicals. Repair mechanisms in mammalian cells following chemical or physical injury are also examined. The Section seeks to quantitate drug metabolism *in vitro* or in experimental animal model systems in order to develop techniques for predicting potentially toxic or carcinogenic reactions of drugs or chemicals in man.

Pregnancy Research Branch (Ronald A. Chez, M.D., Chief) conducts research in the physiology of pregnancy, the effects of disease states on pregnancy, and the identification of those factors which increase perinatal and maternal morbidity and mortality. Extensive resources are available to study perinatal physiology and biochemistry in pregnant baboons, Rhesus monkeys, and sheep as models for human application. The interrelationships of fetal, placental, and maternal polypeptide hormone metabolism, tests of placental function and reserve, and the rate limiting influences on sex steroid production during pregnancy are presently being examined. In addition, the opportunity to obtain experience in other disciplines represented at the National Institutes of Health is available on an individualized basis.

Neonatology Branch (Philip Farrell, M.D., Ph.D., Chief) consists of two sections, neonatology and biochemical genetics.

Section on Neonatology (Philip Farrell, M.D., Ph.D., Head). This Section addresses nutritional studies of premature infants and small for dates infants. There is also research on lung lipid metabolism.

Section on Biochemical Genetics (Joseph Schulman, M.D., Head). Infants and children with different inborn errors of metabolism are investigated, with emphasis on those affecting glutathione metabolism.

Reproduction Research Branch (Kevin J. Catt, M.D., Ph.D., Chief) conducts an integrated program of clinical, biochemical, and biologic studies pertinent to endocrinology and reproductive biology. The Branch accepts three Clinical Associates each year. During the first year, the associate will rotate among the Endocrinology Branches of the NIH to gain a broad knowledge of clinical endocrinology. The next two years are spent primarily in laboratory investigation in collaboration with a senior investigator.

The Branch staffs an Endocrinology Ward and Clinic with emphasis on problems involving the pituitary gland, adrenal cortex, gonads, growth and development. Infertility clinics for men and women are also sources of patients for clinical studies. The laboratory work ranges from studies of proteins and membranes to the physiology and biochemistry of steroid and polypeptide hormones.

Section of Hormonal Regulation (Kevin J. Catt, M.D., Ph.D., Head) places emphasis on the binding and effects of polypeptide hormones such as gonadotropins and angiotensin. Major effects include characterization and isolation of membrane receptors and analysis of the receptor-second messenger systems.

The Social and Behavioral Sciences Branch (Leon J. Yarrow, Ph.D., Chief) engages in research on cognitive, social, and motivational development. Studies in progress have concentrated on the first year of life. Current investigations are concerned with both methodological and theoretical issues regarding early environmental influences, the assessment of neonatal characteristics and effectance motivation.

Among the problems studied are how specific aspects of maternal behavior affect cognitive growth, the development of effectance motivation, and the emergence of the special bond between mother and infant.

Research is underway on reciprocal influences in parent-infant interaction, e.g., the ways in which the infant's early characteristics affect both maternal and paternal behavior. A study is in progress on early father-infant interaction and the father's influence on the mother-infant relationship. A methodological study on the development and expression of attachment in several settings is being carried out.

National Institute of Dental Research

Wallace D. Armstrong, Ph.D., M.D., Acting Director of Intramural Research

Reuben P. Siraganian, M.D., Acting Clinical Director

The National Institute of Dental Research conducts research programs in laboratory, clinical and applied science, germane not only to dental health but also to the broader interests of biology and medicine.

Physicians are appointed for a 2-year period to the Institute's laboratory or clinical programs as Research or Clinical Associates. In general, three Research Associate and two Clinical Associate positions are available annually. Specific program areas, however, will not necessarily have vacancies for Associates in a particular year.

For the most part, dentists will be appointed for 2 years as Dental Clinical Associates, with a dual commitment to research and service as described on page . Dental graduates who possess specialized training and interests applicable to a particular research program of the Institute may also be considered for appointment as Staff Associates, with a full-time assignment to the appropriate laboratory or branch. The number of positions of this type to be filled will be determined solely according to programmatic need.

Minimum qualification for appointment as a Dental Clinical Associate is 1 year of accredited internship, or possession of equivalent advanced training beyond the dental degree. Dentists who have recently completed specialty training will be given particular consideration. Selection will usually be made one year prior to the effective date of appointment. Thus, for example, senior dental students who will enter an accredited internship July 1, 1976, are eligible to apply for an appointment commencing in 1977.

Brief descriptions of the program areas to which Associate appointments are made are provided in the following paragraphs. Additional information about specific programs may be obtained upon request to the Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, Md. 20014.

The Laboratory of Biochemistry (Karl A. Piez, Ph.D., Chief) conducts programs in basic research covering a broad range of biochemical topics. The laboratory has as its objective the investigation of fundamental biochemical processes in normal and disease states.

There are two sections within the laboratory to which an associate may be assigned.

The Protein Chemistry Section (Karl A. Piez, Ph.D., Chief) is concerned primarily with the chemistry and structure of collagen, elastin, and the carbohydrate components of connective tissue. Structure at the molecular level and the interactions that produce higher level tissue structure are determined by chemical, biophysical, and ultrastructural methods.

The Enzyme Chemistry Section (John E. Folk, Ph.D., Chief) is studying the mechanism of action of enzymes using transglutaminases as models. These enzymes produce crosslinks in fibrin during blood clotting, in hair proteins, and in other biological situations. Protein chemical modification, synthesis of substrates, enzyme kinetics, and characterization of the products of crosslinking are used to elucidate the important aspects of enzyme structure and its relationship to catalytic activity.

The Laboratory of Microbiology and Immunology (Stephan E. Mergenhagen, Ph.D., Chief) has as its broad objective the elucidation of the role of microorganisms and immunological mechanisms in oral and systemic health and disease. The basic and clinical programs have application to medical and dental problems and cooperative research with other laboratories is conducted as required by the interdisciplinary nature of particular projects.

NIH Associates are assigned to one of four sections according to the interest of the candidate: Cellular Immunology (Joost J. Oppenheim, M.D., Chief), Humoral Immunity (Ann L. Sandberg, Ph.D., Chief), Clinical Immunology (Reuben P. Siraganian, M.D., Chief), or Microbiology (Charles L. Wittenberger, Ph.D., Chief).

Present projects in immunology encompass the roll of cell-mediated immunity, immune complexes and their effector systems (e.g., complement, vasoactive amines, lymphokines) in acute and chronic inflammatory reactions ultimately related to periodontal diseases, oral mucosal diseases, tissue transplantation, and autoimmune diseases. The microbiological programs include studies on microbial determinants of oral and systemic diseases, bacterial metabolism and its regulation, and taxonomy and ecology of the oral microbiota. Wherever possible fundamental approaches in these disciplines are translated into clinically-oriented or more applied projects through research protocols in clinical immunology as well as through collaboration with the National Caries Program of this Institute.

The LABORATORY OF BIOLOGICAL STRUCTURE (Marie U. Nylen, D.D.S., Chief) is primarily concerned with structural parameters of normal and abnormal function as expressed at varying levels of biological organization, ranging from the subcellular to the organistic. Information is adduced from the application of biophysical and chemical methods, techniques of experimental embryology, as well as from relevant tools of modern histology.

Research and Staff Associates are appointed to the Laboratory and are assigned by mutual agreement to a preceptor in the Molecular Structure Section (E. D. Eanes, Ph.D., Chief) or the Experimental Morphology Section (M. U. Nylen, D.D.S., Chief).

Currently the MOLECULAR STRUCTURE SECTION is engaged in studies on the crystal chemistry of calcium phosphates, the kinetics of mineral nucleation and crystal growth, calcification mechanisms, and the structural chemistry of mineralized matrices. The interests of the EXPERIMENTAL MORPHOLOGY SECTION are divided into two principal areas: (1) the growth and differentiation of mineralized tissues, normal as well as abnormal, and (2) the structure and function of exocrine glands with emphasis on the salivary glands. Opportunities for cooperative research and training are offered in electron microscopy and diffraction, contact and projection microradiography, x-ray diffraction, and infrared and Raman spectrophotometry.

The LABORATORY OF DEVELOPMENTAL BIOLOGY (George R. Martin, Ph.D., Chief) conducts research in (1) normal and abnormal tissue development, particularly craniofacial development and the etiology of anomalies, and (2) on the chemistry, biosynthesis and degradation of oral and other connective tissues.

The CONNECTIVE TISSUE SECTION (George R. Martin, Ph.D., Chief) conducts research on the formation and degradation of connective tissue with particular emphasis on developing structures. It relates the properties of these components to normal and pathological processes.

The CRANIOFACIAL ANOMALIES SECTION (C. T. G. King, Ph.D., Chief) conducts research on the normal development of the craniofacial region and develops animal models of anomalies induced either by genetic or by environmental manipulations, in order to delineate the etiology of the malformation.

The GENETICS AND EPIDEMIOLOGY SECTION (Jerry D. Niswander, D.D.S., Chief) conducts research on the occurrence, behavior, and consequences of normal and abnormal genetic traits with emphasis on oral-facial malformation and malocclusion in human populations and families. Activities include formulation of appropriate mathematical models and development of information concerning procedures appropriate for the control of genetic oral-facial disease and disorders at the population level.

The NEUROBIOLOGY AND ANESTHESIOLOGY BRANCH (Ronald Dubner, D.D.S., Ph.D., Chief) is concerned with the elucidation of basic mechanisms of oral-facial sensation with particular emphasis on pain sensation, and with the development and application of new methods of pain control. Fundamental research on peripheral and central nervous system mechanisms of oral-facial sensation is conducted by the NEURAL MECHANISMS SECTION (Ronald Dubner, D.D.S., Ph.D., Chief). The primary objective of this research group is to correlate behavioral responses to noxious and non-noxious thermal stimuli in the monkey with neuronal structure and function at various levels of the trigeminal system. A multidisciplinary approach is employed and includes the following research activities: (1) electrophysiological studies of the response of single trigeminal nerve fibers and trigeminal brain stem neurons to the noxious and innocuous thermal and mechanical stimuli applied to the oral-facial region of monkeys; (2) neurocytological studies of the receptor, primary afferent, and brain stem organization of the trigeminal system in cat and monkey utilizing light- and electron-microscope techniques; and (3) behavior studies involving pain and temperature discrimination in monkeys trained to avoid potentially noxious or noxious stimuli applied to the face. The NIDR Computer system is utilized for data analysis in the physiological experiments and will provide stimulus control in future behavioral and combined behavioral-electrophysiological experiments.

Applicants for positions in this section should have special training and experience in neurophysiology, neurocytology, experimental psychology, or computer technology.

Clinical research on the development and application of new methods of pain control is conducted by the ANESTHESIOLOGY SECTION (Edward J. Driscoll, D.D.S., Chief). The research objectives and activities of this group include: (1) physiological, pharmacological, and psychological studies of the effects and efficacy of new pharmacological agents utilized in the control of pain in ambulatory dental patients; (2) the development and evaluation of methods of measuring oral-facial pain threshold and tolerance levels; and (3) the development and application of behavioral and other non-pharmacological methods of pain control.

It would be advantageous for applicants for positions in this section to have some training and experience in anesthesiology, pharmacology or psychology.

The Laboratory of Oral Medicine (Abner Louis Notkins, M.D., Chief) conducts basic and clinical research on diseases of the oral cavity. The program is highly interdisciplinary with emphasis on virology, oncology, and endocrinology. The staff includes people trained in medicine, dentistry, and the basic sciences. Present research projects include factors responsible for recurrent and persistent viral infections (e.g., herpes viruses), cellular immunity in viral infections, virus-induced immunopathology, the etiology of various dermatologic disorders including aphthous ulcers, and the role of viruses and other factors in diseases of the exocrine glands (e.g., Sjogren's syndrome, pancreatitis, salivary gland tumors) and endocrine glands (e.g., diabetes mellitus).

The Clinical Investigations Branch (Richard L. Webber, D.D.S., Ph.D., Chief) provides the specialty staff and associated resources for studies, both internally and externally initiated, which are of clinical interest and/or have an interface in the Dental Clinic. A broad spectrum of research activities are encompassed, ranging from theoretical analysis of factors influencing diagnosis and treatment of dental diseases to less sophisticated investigations such as the screening of clinic patients for specific potentially pathogenic microflora. The branch is uniquely suited to such a diverse range of activity by virtue of the wide variety of interests reflected among its dentist, physician, and allied health professional personnel. The availability of NIH-wide research patients from the Clinical Dental Services Section provides a pool of heterogeneous clinical material which is unique in its capacity for both retrospective and prospective control. Current research efforts are directed toward theoretical and applied studies which capitalize on this rare combination of resources.

The Oral Pharyngeal Development Section (James F. Bosma, M.D., Chief) is concerned with investigations of the development of form and of respiratory and feeding functions in normal and in impaired infants and children. Study methods commonly include standard and cephalometric roentgenography, cinephotography, and speech recording. Basic anatomic studies are an integral part of the work of this section. Particular efforts are made to adapt familiar study techniques and therapies to patients severely handicapped by anomaly or by neurologic impairment.

The Clinical Dental Services Section (William E. Wright, D.D.S., Chief) has as its prime function the dual responsibility of providing dental care to the NIH-wide research patient population as well as of providing facilities and supportive activity to all intra-Institute clinical programs. This patient exposure provides a unique opportunity for gaining experience in the observation, treatment, and study of orofacial problems related to a variety of systemic disease. All Dental Clinical Associates are assigned to this section administratively so as to facilitate their service-related activities. However, an individual program is arranged for each associate in order that he may also pursue effectively his clinical and/or basic research interests. This section reports directly to the Clinical Director.

The Diagnostic Methodology Section (Richard L. Webber, D.D.S., Ph.D., Chief) undertakes a variety of research activities which include development of new diagnostic systems based on the application of specific analytical tools, including information theory, linear and nonlinear filter theory, signal detection theory, etc. In addition to determining the role played by analytical factors describing sources of diagnostic information, new methods of data acquisition and management are also under investigation. Opportunities for technically oriented associates of all types, therefore, exist within the multidisciplinary interface unique to this section.

Other related opportunities of a more general nature involve participation in the design and implementation of a variety of research protocols, wherein actual patients are studied on controlled bases to determine the effects of specific therapy on microbial flora and various disease processes.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D., Director

General

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biological factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods; the interaction of multiple agents resulting in enhanced effects; and the modifying effects of variable physical and biological states within man on susceptibility to and course of disease induced by these agents.

There is no single discipline that is unique or specific for the study of environmental health problems. Rather, the distinctive requirement for such research involves the application of a spectrum of skills including biology, biochemistry, bioengineering, biometry and epidemiology, chemistry, pathology, genetics, pharmacology, physics, toxicology, and veterinary sciences.

Location

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, N.C. The National Institute of Environmental Health Sciences is the only one of the 13 Institutes comprising the National Institutes of Health to be located away from the Bethesda, Md., campus.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University at Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, in seminars, and in other scientific and professional activities associated with the universities.

Staff Associates

Staff Associates will work at the National Institute of Environmental Health Sciences under the direction of Dr. David P. Rall, Director, and a Branch Chief in the Institute. Each associate will work directly under a senior scientist in an area of research chosen by the associate and the Institute.

The PHARMACOLOGY BRANCH (L. G. Hart, Ph.D., Acting Chief) studies the toxic effects on mammals and marine species of low level and/or chronic exposure to environmental constituents or contaminants. Interactions (upon or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently underway include: toxication-detoxication systems in liver, lung, skin, and gut—effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in lung and liver; interaction of chemicals at sites of and kinetics of chemical distribution, storage, metabolism, and release—especially in the isolated perfused lung and liver, species differences in xenobiotic disposition and metabolism, pharmacokinetics of pollutant disposition and studies on formation and metabolism of reactive metabolities of hydrocarbons in various marine species; purification and comparison of components of toxication-detoxication systems in various organs; changes in lung components (lipids, proteins, enzymes) as markers of disease or early damage by toxicants, including effects on synthesis and release of lung lipids (surfactant and prostaglandins); incorporation of chemicals into tissue proteins and enzymes and possible importance of these reactions to prolonged tissue storage or allergic reactions to chemicals.

The Pharmacology Branch works extensively with other branches, Institutes and university departments; for example, our researchers in pharmacokinetics collaborate with Environmental Biometry, Environmental Biology and Chemistry, and Environmental Mutagenesis; developmental pharmacology with Environmental Toxicology; toxication-detoxication systems and marine pharmacology with Environmental Mutagenesis, Laboratory of Chemistry, NIAMDD; and lung pharmacology and biochemistry with the Department of Medicine, Duke University.

The ENVIRONMENTAL MUTAGENESIS BRANCH (Frederick J. de Serres, Ph.D., Chief) is responsible for the development of better methodology to test environmental chemical pollutants for mutagenic and carcinogenic activity as well as to monitor the human population to determine whether there is a change in the genetic load. In the first area, research currently underway includes investigation of the role of defective repair systems on inactivation and mutation-induction at specific gene loci, development of test systems in mammals to assay the effects of mutagens on the production of chromosome aberrations and gene mutations *in vitro* and *in vivo*, development of test systems to determine the genetic effect of airborne mutagens as well as the mutagenic effects of chemical carcinogens.

In the second area, method development is focused both on monitoring somatic mutations in peripheral blood cells and in skin fibroblasts, as well as on the detection and measurement of germinal mutations utilizing electrophoretic serum protein variants.

The techniques utilized in the investigations include: manipulation of mutagenic and carcinogenic agents, genetic analysis of microbial organisms, cytochemistry, mammalian tissue culture, autoradiography, cytogenetics, chromatography and ultracentrifugation, and electrophoresis.

The ENVIRONMENTAL TOXICOLOGY BRANCH (Robert L. Dixon, Ph.D., Chief). Scientific efforts of this Branch are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on environmental problems relating to reproduction and development. Toxicologic phenomena are studied from the descriptive to the molecular level in search of a better understanding of mechanisms. This increased understanding contributes to the development of better and more effective test procedures to predict toxicity in humans. Expertise is available in teratology, pharmacology, cell biology, and pathology. Test systems are likewise diverse and range from molecular biochemistry and electron microscopy through *in vitro* cell, organ, and embryo cultures to whole animals. Specific project areas include: (1) environmental factors which affect germ cell development. (2) teratology, (3) transplacental toxicology, (4) development-molecular embryology, (5) development-enzymology and endocrinology-pharmacokinetics, (6) chronic organ toxicology, (7) toxicological test systems development, and (8) effects of environmental agents on learning and behavior.

ENVIRONMENTAL BIOMETRY BRANCH (David G. Hoel, Ph.D., Chief). The mission of the branch is to provide biometrical support for the NIEHS program by employing mathematical and statistical techniques to determine the biological effects of chemical, physical, and biological agents present in the environment. This is accomplished by incorporating in the Institute program statistical principles of experimental design, sampling, and data analysis for both laboratory and epidemiological studies, as well as mathematical analyses of biological systems. Mathematical and statistical procedures are applied and, when necessary, developed to determine the distribution and to estimate the rates of environmentally related diseases among populations, test hypotheses and study the interactions of environmental agents from multi-factor laboratory experiments, and develop mathematical models for describing and predicting biological responses to environmental agents. The branch also provides computer support which ranges from the development of information retrieval and inventory maintenance systems to the simulation of complex biological models. In order to accomplish the mission of the Biometry Branch the following areas of activity are identified: (a) Analytical Statistics, (b) Epidemiology, (c) Mathematical Statistics, (d) Biomathematics, (e) Computer Programming, and (f) Data Processing.

ENVIRONMENTAL BIOPHYSICS BRANCH (J. R. Fouts, Ph.D., Acting Chief) is involved in several studies on the biological effects of physical factors in man's environment. At present, the programs concentrate on biological effects of microwave radiation and noise singly and in combination with other factors. Microwave effects on reproduction and nerve functions (both isolated nerves and activities of the central nervous system as reflected in behavior) are under study. Noise effects on various inner ear functions are being studied in combination with ototoxic drugs and heavy metals. Newer methods have been developed for quantifying microwave doses and for studying sound effects on inner ear physiology and biochemistry. This development of methods and application of biophysical technics to studies of environment-caused injury is an important aspect of the Branch programs.

The ENVIRONMENTAL BIOLOGY AND CHEMISTRY BRANCH (John A. Moore, D.V.M., Chief) maintains collaborative support laboratories in the disciplines of chemistry, inhalation toxicology, comparative pathology, immumology, and veterinary medicine, and plans and conducts research appropriate to the functions of branch laboratories. Current research programs include studies on the effect of environmental chemicals on immune competence and pulmonary structure and function; characterization of the toxic effect of the chlorinated dibenzodioxins, dibenzofurans, and polychlorinated biphenyls; development of immunoassay methods; and instrumental methods, particularly mass and magnetic resonance spectrometric techniques to identify environmental chemicals and their transformation products.

National Institute of General Medical Sciences

Byron B. Clark, Ph.D., Director of the Pharmacology Research
Associate Program

Pharmacology Research Associates

This Institute has positions available each year for Pharmacology Research Associates. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of the National Institutes of Health, under the Pharmacology Research Associate Program.

The program is directed to those who have already made a commitment in pharmacology by training or research in the field.

Associates will study principles of pharmacology and toxicology and the application of physical and chemical concepts to pharmacology. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also available. During their tenure, Pharmacology Research Associates devote the larger portion of their time to laboratory research in the biomedical sciences, with no clinical responsibilities.

The objective of the Program is to develop leaders in pharmacology research for key positions in academic, industrial, and governmental research laboratories.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance both the work in progress and the competence of the prospective independent investigator. Preceptors and Research Associates are matched by a mutual selection procedure after personal interviews.

Associate candidates include those who will have received either the Ph.D. or M.D. degree and have research experience in pharmacology or toxicology. They may also include those with research experience in a related area but who wish to further their development in pharmacology. M.D. candidates may use this opportunity to further their training in basic pharmacological research in preparation for a career in clinical pharmacology or a related discipline. Each of the following Institutes of the National Institutes of Health participates in the Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

National Cancer Institute

LABORATORY OF CHEMICAL PHARMACOLOGY—Richard H. Adamson, Ph.D.

The general areas being studied include (1) the physiological disposition of antitumor agents; (2) structure-activity relationships (SAR) of antitumor agents; (3) new approaches to cancer chemotherapy and therapeutics in general, including studies with polymers and the nature of drug receptors; (4) comparative pharmacology; and (5) induction of tumors in nonhuman primates with carcinogens and/or virus and chemotherapy of these tumors.

LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY —David G. Jones, M.D., Ph.D.

Research is carried out on the pharmacology of cancer chemotherapeutics and related agents, and includes studies on the mode of action, physiological disposition and metabolism of this group of drugs. Of special concern are agents which act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the methotrexate:dihydrofolate reductase and 5-FdUMP:thymidylate synthetase interactions. Other areas of investigation include the role of enzyme induction in drug resistance; the effects of inhibition and enhancement of rates of drug metabolism on pharmacological activity; the physiological disposition of the rifampicin group of DNA- and RNA-polymerase inhibitors; and the role of the hepatic metalloflavoprotein aldehyde oxidase in the metabolism of N-heterocyclic compounds.

LABORATORY OF TOXICOLOGY—Theodore E. Gram, Ph.D.

The general area of research is in the factors which contribute to the termination of drug action, including metabolism and biotransformation of drugs and other xenobiotics, and enzymatic mechanisms controlling drug oxidation and conjugation in both hepatic and extra-hepatic tissues. Other areas of interest are the effects of biologically active antineoplastic agents on the metabolism of other drugs and the possible effects of enzyme induction or inhibition on the biological activity of oncolytic agents. In addition, work is underway in the area of drug-induced pneumotoxicity. A number of oncolytic drugs, including bleomycin, busulfan, methotrexate, and other drugs and xenobiotics induce a progressive pulmonary fibrosis in animals and in man which terminates in death due to pulmonary insufficiency. Studies are being started to investigate the pathologic insults involved at stages prior to actual increases in pulmonary collagen biosynthesis and the possibilities of arrest, reversibility, or even prophylaxis of this life threatening problem.

CHEMISTRY BRANCH—Harry V. Gelboin, Ph.D.

Research is being conducted on the molecular biology of microsomal enzyme regulation. Cell culture systems are used to study the mechanism of enzyme induction, the hydroxylation of polycyclic hydrocarbons, and the relationship of the microsomal enzyme system to drug action and carcinogenesis.

LABORATORY OF EXPERIMENTAL CHEMOTHERAPY—Abraham Goldin, Ph.D.

The program is concerned with the investigation of the mode of action of anticancer agents. Areas of investigation include: drug action in relation of cell cycle kinetics; metabolite-antimetabolite interrelationships in chemotherapy; combination chemotherapy with reference to drug potentiation and therapeutic synergism; adjuvant and immunochemotherapy; mechanisms and therapy of tumor cell resistance to drugs; tumor invasiveness and metastasis; structure-activity relationships of antitumor agents; chemotherapy of transplantable, carcinogen and viral induced, and spontaneous tumors; molecular biological and pharmacological investigation of the mechanism of action of antitumor agents. The laboratory program is closely related to clinical interests, and an attempt is made to establish therapeutic principles for transference to clinical chemotherapy.

EXPERIMENTAL THERAPEUTICS PROGRAM—Vincent T. Oliverio, Ph.D.

Studies are generally related to the pharmacological disposition of antitumor agents and other drugs in man and animals through the use of established and newly developed analytical-biochemical techniques.

Particular emphasis is placed on the study of (a) the influence of simultaneously administered drugs on the distribution, protein binding, metabolism, renal clearance, and therapeutic activity of the individual agents, (b) the pharmacokinetics of the entry of drugs across membranes into sensitive and resistant tumor cells, and (c) the carcinogenic and other toxicological effects of drugs. Drugs of recent interest have been the folic acid antagonists, nitrosoalkylureas, substituted hydrazines, and plant alkaloids.

LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY—Marco Rabinovitz, Ph.D.

Investigations in this laboratory are concerned with the characterization of structures and functions of cells which contribute to their resistance to selected cancer chemotherapeutic agents. Analytical procedures are devised to study sensitive and resistant cell lines with regard to receptor sites and agent metabolism. Such information permits the introduction of pharmacological and nutritional regimens to counteract or augment the observed sensitivity or resistance.

The laboratory operations include tissue culture, use of tumor-bearing animals, radioactive tracer techniques, and the synthesis of appropriately modified agents or synergists.

National Institute of Dental Research

LABORATORY OF DEVELOPMENTAL BIOLOGY AND ANOMALIES—George R. Martin, Ph.D.

Individuals in this laboratory are studying the steps in normal and abnormal development. THE CONNECTIVE TISSUE SECTION emphasizes studies on the formation of these tissues. The SECTION ON CRANIOFACIAL ANOMALIES uses drug induced abnormalities to probe normal development.

National Institute of Mental Health

LABORATORY OF CLINICAL SCIENCE—Julius Axelrod, Ph.D.

The SECTION ON PHARMACOLOGY is engaged in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of drugs, biogenic amines, and enzymes; the distribution and metabolism of drugs, the isolation and characterization of enzymes involved in drug and biogenic amine metabolism. In addition, the laboratory is engaged in examining control mechanisms of the biochemistry of the pineal gland and biological rhythms.

LABORATORY OF CLINICAL SCIENCE—David M. Jacobowitz, Ph.D.

The SECTION ON HISTOPHARMACOLOGY is involved with studies of monominergic nerves (noradrenergic, dopaminergic, serotonergic), cholinergic nerves, and gabaminergic nerves in the brain and the peripheral autonomic nervous system. A multidisciplinary approach is used to correlate localization of central monominergic and cholinergic nerves with function. Histochemical, biochemical, and behavioral studies are currently underway. Using the catecholamine histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions is used to correlate changes in neuronal function with various parameters of behavior. Measurements of associated neuronal amines and enzymes are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a micropunch method and radioisotopic assays. Immunofluorescence methods are being used to study the localization of various enzymes in nerves. The growth of nerves is also studied using tissue and organ cultures.

LABORATORY OF CLINICAL SCIENCE—Irwin J. Kopin, M.D.

The research efforts of the SECTION ON MEDICINE are centered around the study of biochemical and physiological effects of drugs and toxins which alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes which control their synthesis in both the central and peripheral nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures.

Procedures are developed for application to clinical studies to evaluate neurotransmitter and neuroendocrine function in human subjects with various neuropsychiatric disorders during administration of psychoactive drugs. Plasma, urine, and CSF are analyzed for various drugs, amines, and metabolites, and their rates of utilization or synthesis determined using radioimmunological enzymatic, or mass spectroscopic techniques.

LABORATORY OF PRECLINICAL PHARMACOLOGY—Erminio Costa, M.D.

This laboratory conducts a program of research in neurochemistry and neuropharmacology to elucidate the molecular nature of the mechanisms whereby various psychoactive drugs affect various neuronal systems. Current research includes: (1) the molecular regulation of postjunctional receptors with particular regard to the biochemical reactions occurring at the neuroeffector junction in response to the release from nerve terminals of catecholamines, serotonin, GABA, acetylcholine, and polypeptides which function as putative neurotransmitters; (2) the molecular nature of short term regulation of rate-limiting enzymatic reactions controlling the dynamic equilibrium of neuronal monoamines at synapses; (3) the regulation of acetylcholine metabolism as it relates to changes in neuronal function; (4) the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin, and GABA by mass fragmentography and to study drug actions at the synaptic level; (5) the role of cyclases, phosphodiesterases, phosphoprotein phosphatases, and protein kinase activation and translocation in the trans-synaptic regulation of gene expression in postsynaptic cells.

LABORATORY OF NEUROCHEMISTRY—Seymour Kaufman, Ph.D.

The main effort of the laboratory is concerned with the study of a group of enzymes that are involved in the oxidative metabolism of the aromatic amino acids. These enzymes include phenylalanine hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, and dopamine β-hydroxylase. These enzymes play unique roles - either directly or indirectly - in the normal development and functioning of the central nervous system. Phenylalanine hydroxylase, for example, occurs only in the periphery but its lack, as in the disease phenylketonuria, affects exclusively the CNS. The other enzymes catalyze key reactions in the biosynthesis of neurotransmitters, dopamine, norepinephrine and serotonin. One of the goals is to understand how the properties of these enzymes - catalytic, physical, and regulatory - determine their activity within the cell. The regulatory properties of these enzymes are being examined at various levels of tissue organization and include studies with highly purified enzymes, as well as those with cell suspensions, tissue slices and whole animals. One of the areas of current emphasis is the study of aspects of the enzymology of phenylketonuria and its variants in cultured fibroblasts.

LABORATORY OF CEREBRAL METABOLISM—Louis Sokoloff, M.D.

The Laboratory of Cerebral Metabolism carries out a broad program of investigations on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the central nervous system. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones, which play important physiological roles in CNS function. Present emphasis is on the mechanism of action of thyroid hormones, not only on the maturation of the nervous system, but also on metabolic processes in all susceptible tissues. A method has recently been developed in this laboratory which permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiological and pathological states.

LABORATORY OF GENERAL AND COMPARATIVE BIOCHEMISTRY—Werner A. Klee, Ph.D.

The major emphasis of our current program is directed towards the elucidation of the mechanism of action of opiates and the peptides which normally interact with opiate receptors. Included in this program are studies on the isolation and characterization of opiate receptors, of endogenous morphine-like factors, and of the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in tissue culture, are aimed at understanding narcotic tolerance and dependence as well as analgesia and euphoria in biochemical terms. The relevance of this work to the action of other CNS active drugs and to normal brain function is also being explored.

LABORATORY OF NEUROPHARMACOLOGY—Forrest F. Weight, M.D.

The research investigations in this laboratory have been on the pharmacology of single neurons and synapses in the central and peripheral nervous system. Recently this has included the role of cyclic nucleotides in synaptic function. The research techniques offered are: (1) extracellular iontophoresis (microelectrophoresis) of drugs and chemicals to single neurons, (2) intercellular recording from single neurons, (3) intracellular iontophoresis of drugs and chemicals, (4) intracellular pressure injection of drugs and chemicals, (5) biophysical methods (such as conductance change and reversal potential) of investigating the mechanism of a drug's action on a neuronal membrane, and (6) extracellular ion changes to study the nature of permeability change of the membrane produced by a drug.

LABORATORY OF PRECLINICAL PHARMACOLOGY—N. H. Neff, Ph.D.

The section on biochemical pharmacology is concerned with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine containing neuron. Current studies are directed towards: (1) characterization of enzymes involved in amine metabolism; (2) biochemical evaluation of receptor responses; (3) evaluation of the mechanism of action of drugs that alter neuronal function; and (4) the possible role of the biogenic amines in various disease states.

National Institute of Arthritis Metabolism and Digestive Diseases

LABORATORY OF CHEMISTRY—John W. Daly, Ph.D.

The SECTION ON PHARMACODYNAMICS is engaged in research on the formation, degradation, and role of cyclic nucleotides in the central nervous system. The interrelationships between functional states of central neuronal networks and the responsiveness of cyclic nucleotide-generating systems to specific agents such as catecholamines, serotonin, histamine, adenosine, glutamate, GABA, etc.; the physiological role and mechanism of action of adenosine and membrane depolarization in regulation of cyclic AMP formation; and the morphological entities in brain slices associated with cyclic nucleotide formation in response to specific agents represent some aspects of this research.

ARTHRITIS AND RHEUMATISM BRANCH—Elizabeth Neufield, Ph.D.

Research is in the general area of human biochemical genetics, studied in cell culture. Of immediate interest are disorders of enzyme localization. For instance, in I-cell disease many hydrolytic enzymes are extracellular instead of intralysosomal. Such mutations lead to an understanding of the normal mechanism for packaging enzymes in their appropriate organelles.

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Herbert Tabor, M.D.

The work is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biological materials, and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Future work will be directed, in part, toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (e.g., enzyme characterization, bacteriophage, nucleic acid chemistry, isotopic and nonisotopic synthesis). The amino acid studies are concerned with the induced enzymes involved in histidine degradation, and their use as tools in studying induction, repression, and enzyme mechanisms. Other work in the laboratory includes studies on control mechanisms for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability.

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Loretta Leive, Ph.D.

This laboratory investigates the structure, assembly, and function of membranes. One area of study is the mechanism whereby gram-negative organisms resist drugs that attack gram-positive organisms. It was found that the gram-negative outer membrane excludes these drugs, and that the lipopolysaccharide of the membrane participates in this barrier function. Treatments that increase permeability and mutants altered in outer membrane components or permeability are being used to analyze the mechanisms involved. This research may suggest ways of increasing drug sensitivity in gram-negative organisms. Another area of study concerns mechanisms by which membranes assemble. The outer membrane appears heterogeneous, with areas specialized for insertion of new molecules, and the rates and mechanisms of insertion and rearrangement are being studied. These studies, in a system susceptible to genetic manipulation and with a relatively simple membrane, may help elucidate such properties, which are basic to membranes in general.

Molecular Disease Branch—W. French Anderson, M.D.

The Section on Molecular Hematology investigates the mechanism and regulation of hemoglobin biosynthesis. Studies include the isolation and characterization of animal and human messenger RNA for hemoglobin, cell-free protein-synthesizing systems, the mechanism of initiation of protein synthesis, RNA transcription, cell fractionation, tissue culture of bone marrow cells, somatic cell hybridization, and patient investigations. Under direct investigation are the thalassemias, hemoglobinopathies, and other types of hemolytic anemias.

Cardiology Branch—Stephen E. Epstein, M.D.

The research objectives of this branch are oriented primarily toward an elucidation of the physiological and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacological interventions on the heart and peripheral circulation. Projects include pharmacologic, physiologic, and biochemical studies in man, intact animals, and smooth muscle cells grown in culture. Major emphasis is on the study of (1) the mechanisms responsible for arrhythmias and myocardial cell-death in acute myocardial infarction and their prevention, and (2) an understanding of the physiological and biochemical factors stimulating the atherosclerotic process.

Laboratory of Chemical Pharmacology—James R. Gillette, Ph.D.

The Section on Drug-Enzyme Interaction studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objective has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal level.

Laboratory of Chemistry—John J. Pisano, Ph.D.

The Section on Physiological Chemistry, Laboratory of Chemistry, studies normal and pathological states in man at the molecular level. Under investigation are the prostaglandins, neuroactive and vasoactive peptides (e.g., bradykinin and angiotensin), precursor proteins of the peptides and the enzymes involved in their biosynthesis and degradation. Modern analytical techniques such as gas chromatography, high performance liquid chromatography, affinity chromatography, mass spectrometry and radioimmunoassay are commonly used. Research is currently directed to the study of hypertension, coagulation, and fibrinolysis, micro methods for the detection of polypeptides and analysis of their amino acid sequence, and the discovery of naturally occurring biologically active peptides.

Hypertension-Endocrine Branch—Walter Lovenberg, Ph.D.

The research of the Section on Biochemical Pharmacology is directed toward an understanding of mechanisms and regulation of monoamine neurotransmitter synthesis and the relationship of monoaminergic systems to specific diseases. Some of our current projects are: (1) molecular mechanisms of short- and long-term regulation of tyrosine hydroxylase activity; (2) chemical, structural and biosynthetic studies on dopamine-β-hydroxylase; (3) molecular events in the transduction of nerve impulses into changes in target cell proteins and enzyme levels; (4) the mechanism and regulation of serotonin synthesis in the CNS; (5) *in vivo* and *in vitro* studies on the mechanism of centrally active drugs; (6) the role of central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields including pharmacology, enzymology, protein chemistry, and molecular biology.

Laboratory of Biochemical Genetics—Marshall Nirenberg, Ph.D.

The Section on Molecular Biology is conducting studies on clonal cells derived from the nervous system including those that are of normal and neoplastic origin as well as somatic cell hybrids. The objectives are to identify the molecules and the reactions that enable cells to communicate with each other, via synaptic junctions, and to investigate the problem of how genes determine neuron sequence as neurons are assembled into circuits during embryonic development. Work would involve predominantly biochemistry, mammalian cell cultures, cyclic nucleotide enzymology, cell receptors, and enzymes of neurotransmitter metabolism.

Hypertension-Endocrine Branch—Harry R. Keiser, M.D.

The Section on Experimental Therapeutics offers a spectrum of research opportunity ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins, and catecholamines conducted both in man and in experimental animals. Other current studies encompass disorders of serotonin and histamine.

Laboratory of Biochemical Genetics—Alan Peterkofsky, Ph.D.

The Section on Macromolecules is currently concentrating on studes of cellular control mechanisms. The major focus of interest at present s the control of the synthesis and metabolism of cyclic nucleotides in acterial cells. The current information suggests that cyclic AMP concenrations in *E. coli* are controlled by cellular metabolites by a mechanism imilar in some respect to that by which hormones affect cyclic AMP levels n many mammalian cells. Another current area for study involves the nechanisms of some unusual aspects of protein synthesis in mammalian ystems, e.g., N-terminal modification of immunoglobulins and/or albunin, as well as the biosynthesis of the tripeptide thyrotropin releasing actor.

ABORATORY OF CHEMICAL PHARMACOLOGY—Hypertension-Endocrine Branch—Jerry R. Mitchell, M.D., Ph.D.

Research in this laboratory centers around the isolation and identificaion of drugs, drug metabolites, and endogenous substances (steroids, prostaglandins, monoamines) from biological fluids, and the study of their rates of formation and disposition (pharmacokinetics). Additional studies examine the oxidative mechanisms by which monooxygenases or superoxide anion convert chemically stable drugs to highly reactive imidoquinones, free radicals, and other toxic electrophiles. Possible cause-effect relationships are examined between these determinants and drug-induced tissue lesions (e.g., acetaminophen, phenacetin, furosemide, isoniazid, or methyldopa hepatic and renal injury), drug therapy (e.g., propranolol concentrations and hypertension control), or disease processes (e.g., pathogenetic role of various steroids in low-renin hypertension). Routine procedures include chemical synthesis of radioactive and stable-isotope analogs (e.g., for quantitative mass fragmentography), and drug analysis by t.l.c., g.c., l.c., mass spectrometry or radioimmunoassay.

PULMONARY BRANCH—Elwood O. Titus, Ph.D.

The SECTION ON MOLECULAR PHARMACOLOGY studies the mechanism of interaction of drugs and hormones with membrane receptors important in the regulation of cellular function. Topographical or conformational changes associated with binding of drugs or humoral agents to individual proteins are measured by physical chemical techniques including electron spin resonance and nuclear magnetic resonance, circular dichroism, fluorescence spectroscopy, etc. Efforts to isolate receptor substances are carried out. Some work on the pharmacology of isolated tissues is performed as needed for correlation of physiological effects with changes in membrane chemistry. Current studies deal with the characterization of membrane receptors for neurohumoral agents, the relationship between various receptors and ion transport mechanisms and with the role of conformationally mobile sites on membrane proteins in the regulation of ion transport by cardiac glycosides. Affinity labels and double isotope procedures are used to characterize various types of receptors.

PULMONARY BRANCH—Michael A. Beaven, Ph.D.

The SECTION ON MOLECULAR PHARMACOLOGY has a broad interest in local tissue hormones, the biogenic amines (histamine, serotonin, and the catecholamines), the polyamines (putrescine, spermine, and spermidine) the prostaglandins, and the enzymes involved in the synthesis and degradation of these substances. The work is concerned with the role of these compounds in health and disease. Investigations have included: (1) the study of polyamines in tissues with rapid cell turnover, e.g., thymus lymphocytes, regenerating liver, and various tumors; (2) the release and synthesis of histamine, serotonin, and other tissue factors in inflammator and allergic reactions in *in vivo* and *in vitro* systems; and (3) the effect o anti-inflammatory drugs in cell growth, metabolic activity in various mammalian cell culture systems. Current studies are directed toward the role o biogenic amines in lung and include investigations of the influence of age infection, and allergic conditions on the synthesis and turnover of histamine and serotonin in lung. Normal and germ-free animals are being use for these studies. The work requires the use of sensitive isotopic assa procedures and particular emphasis is given to the possible use of thes procedures in the diagnosis of disease.

PULMONARY BRANCH—Colin F. Chignell, Ph.D.

The SECTION ON MOLECULAR PHARMACOLOGY is concerned with the mechanism of drug action at the molecular level. Drug interactions with biological systems are being studied with a variety of physical and spectroscopic techniques including ultraviolet and visible absorption spectroscopy, fluorescence spectroscopy, nuclear magnetic resonance and electron spin resonance (including the use of spin labels), and optical rotatory dispersion and circular dichroism. Current areas of active research include the binding of drugs to plasma proteins, nucleic acids, membranes, and other cellular components, the binding of colchicine and its analogs to microtubule protein, the interaction of decamethonium and hexamethonium with acetylcholinesterase and acetylcholine receptor protein from *Torpedo californica*, and the inhibition of mammalian erythrocyte carbonic anhydrase by aromatic sulfonamides. Other projects are concerned with the mechanism of drug-induced phototoxicity and photoallergy and the characterization of lung surfactant lipoprotein.

LABORATORY OF CELLULAR METABOLISM—Martha Vaughan, M.D.

Major areas of research interest are (1) the mechanisms underlying hormonal control of lipolysis in fat cells, with emphasis at present on characterization of the hormone-sensitive lipase and elucidation of manner in which insulin, prostaglandins, and adrenal steroids affect the formation, degradation, and action of cyclic AMP, and (2) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides (e.g., prostaglandins, adrenal steroids) in regulation of growth and morphology of mammalian cells grown in culture, and (3) the nature and regulation of guanylate cyclases in smooth muscle and other cells.

National Institute of Allergy and Infectious Diseases

LABORATORY OF PARASITIC DISEASES—Eugene Weinbach, Ph.D.

The effects of drugs and other toxic agents on the metabolism of mitochondria are studied to provide a biochemical basis for their pharmacological activity. Current studies are concerned with electron transport, oxidative phosphorylation, ion translocation, and structure-function relationships in mitochondria. Particular attention has been given to compounds that uncouple oxidative phosphorylation and to their mechanism of action. A hypothesis concerning the mechanism of uncoupling of oxidative phosphorylation based on conformational changes in proteins involved in energy conservation has been derived from these studies. The work will be extended to determine if other pharmacologically active agents induce conformational changes in proteins and thereby alter their catalytic function.

National Institute of Child Health and Human Development

LABORATORY OF BIOMEDICAL SCIENCES—David C. Klein, Ph.D.

Investigations within the SECTION ON PHYSIOLOGICAL CONTROLS have focused on describing the molecular mechanisms through which hormones and biogenic amines regulate gene expression. The role of cyclic AMP in the regulation of the activity of enzymes and the regulation of indole metabolism has been one of the major areas of interest. Current research is concerned with the relationship between biogenic amines and the production and release of peptide hormones from neuroendocrine tissue. In addition, enzyme induction is being studied using biochemical and electrophysiological tools to understand the relationship between the biochemical and electrophysiological effects of neurotransmitters.

BEHAVIORAL BIOLOGY BRANCH—Phillip G. Nelson, M.D., Ph.D.

The BEHAVIORAL BIOLOGY BRANCH conducts research in neurobiology using tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress.

DEVELOPMENTAL PHARMACOLOGY BRANCH—Daniel W. Nebert, M.D.

This branch investigates the molecular mechanisms underlying genetic differences and environmental factors influencing drug metabolism in man. The program includes a search to understand congenital malformations, the toxic or mutagenic or carcinogenic effect of drugs, the development of drug-metabolizing enzymes and their capacity to be induced or repressed, and jaundice caused by breast milk feeding. Genetics in mice and cell culture techniques are commonly used as experimental model systems. Attempts are being made to distinguish genetic factors from environmental influences and to develop methods for assessing or predicting a compound's teratogenic, toxic, mutagenic, or carcinogenic effect in man. This research complements and supports the on-going Institute programs in the Pregnancy Research Branch and the Neonatal and Pediatric Medicine Branch. Intent is to form an overall Perinatal Biology Program which will span the health concerns of children and mothers during both the prenatal and postnatal periods.

National Institute of Environmental Health Sciences

PHARMACOLOGY BRANCH—James R. Fouts, Ph.D.

Research Programs: Inhalation Toxicology - exposures of animals to various mixtures of vapors, aerosols, particles, etc., and evaluation of mechanisms of damage, especially to the lung. *Pulmonary Group* - use of isolated perfused lung in study of chemical uptake and effect of chemicals on nonrespiratory functions, lung physiology, and biochemistry. Collaboration with clinical groups at Duke University on chemical-induced lung disease. *Pharmacokinetics* - whole animal and isolated organ studies of rates and mechanisms of chemical uptake, storage, and release. Collaboration with DCRT, NCI groups in Bethesda. *Marine Pharmacology* - studies of mechanisms of pollutant accumulation in edible marine species; use of marine systems to detect waterborne pollutants. Field labs in Maine and Florida; interagency collaborative efforts, collaboration with university scientists here at NIEHS as well as in Maine and Florida. *Toxication-*

Detoxication - toxication-detoxication systems in hepatic versus extrahepatic tissues, species differences, developmental patterns; role of metabolic activation of chemicals in mutagenesis, teratology.

ENVIRONMENTAL TOXICOLOGY BRANCH—Robert L. Dixon, Ph.D.

The scientific efforts of this branch are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on environmental problems relating to reproduction and development. Toxicologic phenomena are studied from the descriptive to the molecular level in search of a better understanding of mechanisms. This increased understanding contributes to the development of better and more effective test procedures to predict toxicity in humans. Test systems are diverse and range from molecular biochemistry and electron microscopy, through *in vitro* cell, organ, and embryo cultures, to whole animals. Specific project areas include the following: (1) Mechanisms of abnormal embryonic development (teratology; transplacental toxicology), (2) Perinatal enzymology and immunology (biochemical indicators of developmental toxicology), (3) Mechanisms and toxicity of hormonally active chemicals, and (4) Gene expression and macromolecular synthesis during embryonic development.

The Pharmacology Research Associate Committee

Choice of program area depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. The Pharmacology Research Associate Committee offers counseling to applicants invited to the NIH for interviews.

National Institute of Mental Health

John C. Eberhart, Ph.D., Director of Intramural Research
Robert A. Cohen, M.D., Ph.D., Director, Division of Clinical and Behavioral Research

This Institute offers an opportunity for postdoctoral research training in psychiatry and in the biological and behavioral sciences. Clinical Associates are assigned clinical responsibility in caring for patients who are admitted for both therapeutic and research purposes. Research Associates engage in laboratory research in one of the biological or behavioral science laboratories under the preceptorship of one of the senior staff, and may in addition participate in tutorial seminars and other teaching programs, as their needs and desires indicate.

Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all associates to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Descriptions of the NIMH program areas to which associates will be appointed follow.

The Adult Psychiatry Branch (W. E. Bunney, Jr., M.D., Chief; Senior Staff: Dr. G. L. Brown, Dr. M. Buchsbaum, Dr. E. Gershon, Dr. C. Gillin, Dr. R. M. Post, Dr. D. P. van Kammen, Dr. R. Wyatt, Dr. J. Tallman, Dr. C. Pert, and Dr. A. Pert) conducts a broad program of research and training in clinical and biological aspects of psychiatry, including psychological, genetic, pharmacological, and biochemical investigations of mania, depression, schizophrenia, and childhood mental illness. Ordinarily, 2 years of clinical psychiatric residency training should precede arrival on duty; for Clinical Associates, the program is accredited for third-year psychiatric residency training. Current research projects include: (1) assessment, treatment, and followup of acute schizophrenic patients and their families; (2) biological correlates (sleep, activity, biogenic amines and related enzymes, and endocrine function) in acute schizophrenic, manic-depressive, drug-induced psychoses, and childhood mental illness; (3) mechanisms of action of psychotropic and addictive drugs; (4) clinical assessment of new psychotherapeutic drugs and treatment modalities; (5) genetic studies of biological, pharmacological, and personality characteristics of patients with affective disorders and their relatives, and development of models of genetic transmission of biochemical and pharmacologic outpatient clinic studies of the well state in affective disorders; (6) perceptual psychophysiology, biogenic amines, and attention using computer and averaged evoked potential techniques; (7) investigation of behavioral pharmacology, models of depression and schizophrenia, CNS and spinal fluid physiology and biochemistry in subhuman primates; (8) studies of the physiology, biochemistry, and pharmacology of receptor function in animals and man.

The Laboratory of Clinical Science (Irwin J. Kopin, M.D., Chief; Senior Staff: Dr. Julius Axelrod, Dr. Michael H. Ebert, Dr. Frederick K. Goodwin, Dr. David M. Jacobowitz, and Dr. Dennis Murphy) conducts a program of research in biochemistry, pharmacology, physiology, medicine, and psychiatry and the interrelationships between them. Current research includes: (1) mechanism of action and metabolism of drugs and hormones which act in the nervous system; (2) biochemical studies in endocrine and metabolic disorders of amino acids, catecholamines, and other biogenic amines; (3) clinical pharmacology including drug metabolism; (4) longitudinal investigation of patients (acute or episodic psychosis, depression) stressing biological factors (endocrine function, catecholamines, serum proteins, specific enzyme activities); (5) biological rhythms and thei control; (6) biological aspects of toxic psychoses and drug addiction; an (7) relationship of biogenic amines to neuropsychiatric disorders.

The Laboratory of Neurobiology (Ichiji Tasaki, M.D., Chief; Senio Staff: Robert H. Wurtz, Ph.D.) conducts research on the nervous system a several levels ranging from biochemical and biophysical studies of single excitable cells to studies of systems of neurons in the brain. Current research projects include studies on: (1) the excitation process in nerve and muscle membrane using recently developed optical techniques to demonstrate changes in birefringence, absorbance, and fluorescence in excitable tissue during an action potential; (2) biophysics of model membrane systems; and (3) the integration in the brain of visual information and extravisual input (such as eye movements and attention) using single unit recording in awake monkeys performing a learned task.

The LABORATORY OF GENERAL AND COMPARATIVE BIOCHEMISTRY (Giulio L. Cantoni, M.D., Chief; Senior Staff: Werner A. Klee, Ph.D., Carl R. Merril, M.D., Stuart H. Mudd, M.D.) conducts investigations on: mechanisms and pathways of protein biosynthesis; biological methylations; alkaloid biosynthesis; differentiation and gene expression in eukaryotes.

The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, RNAse action, mechanism of drug addiction, muscle differentiation in cell culture, and transgenosis.

The SECTION ON ALKALOID BIOSYNTHESIS studies the enzymes involved in alkaloid biosynthesis, their control and biosynthesis in relation to morphogenetic development of the plant; also, enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

The LABORATORY OF CEREBRAL METABOLISM (Louis Sokoloff, M.D., Chief; Senior Staff: Marian W. Kies, Ph.D., Russell E. Martenson, Ph.D., Elaine E. Kaufman, Ph.D., and Charles Kennedy, M.D.) The Section on Developmental Neurochemistry conducts a broad program of investigations on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the central nervous system. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones, which play important physiological roles in CNS function. Present emphasis is on the mechanism of action of thyroid hormones, not only on the maturation of the nervous system, but also on metabolic processes in all susceptible tissues. A method has recently been developed in this laboratory which permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiological and pathological states.

The LABORATORY OF NEUROCHEMISTRY (Seymour Kaufman, Ph.D., Chief; Senior Staff: Howard A. Nash, M.D., David M. Neville, Jr., M.D., and Audrey L. Stone Ph.D.) conducts investigations in the following areas: (1) the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine hydroxylating system. In addition to studies with the pure enzymes, there is emphasis on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia; (2) the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin and the relationship between the properties of the enzymes and physiological regulation of rates of synthesis of these neurotransmitters; (3) the biochemical basis for skeletal muscle hypertrophy including the effects of exercise and neural factors in the process; (4) cell surface membrane proteins and receptors in their role in cellular differentiation; and (5) the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

The LABORATORY OF NEUROPHYSIOLOGY (E. V. Evarts, M.D., Chief; Senior Staff: Frederick A. Miles, Ph.D. and Stanley I. Rapoport, M.D.) conducts research on (1) neural control of movement; (2) plasticity of stimulus-response relations; (3) the physiology and pharmacology of the blood-brain barrier; and (4) metabolic correlates of brain activity.

The studies on neural control of movement are designed to elucidate the functional interrelations between motor subsystems (e.g., spinal cord, brain stem, cerebellum, basal ganglia, thalamus, and cerebral cortex). This work involves behavioral, electrophysiological, and neuroanatomical techniques. Projects are aimed at understanding both reflex and voluntary motor function. Studies on control of eye movements focus both on the vestibulo-ocular reflex and on saccadic movements. Discharges of single nerve cells are recorded with microelectrodes in monkeys trained to carry out movements, and the results are interpreted in relation to the anatomical input-output properties of the loci from which recordings are obtained.

Work in the area of plasticity of stimulus-response relations involves: the role of segmental and suprasegmental neural factors in determining the modifications of muscular activity associated with motor learning in man and subhuman primates. Studies also focus on mechanisms underlying adaptive changes in the vestibulo-ocular reflex in the monkey.

The blood-brain barrier, which regulates cerebral metabolism and function, is opened reversibly for experimental pharmacology, its structure at cerebral blood vessels is elucidated with electron microscopy, and the principles regulating transport are determined by experimental and theoretical means.

Increased neuronal activity is associated with increased neuronal metabolism, and techniques for detecting localized changes in cerebral metabolism are now being used to discover the location and magnitude of metabolic changes associated with a variety of different cerebral functional states. Studies are currently focused on discovering cerebral metabolic processes underlying sleep and motor behavior.

The LABORATORY OF BRAIN EVOLUTION AND BEHAVIOR (Paul D. MacLean, M.D., Chief; Senior Staff: John B. Calhoun, Ph.D., and Walter C Stanley, Ph.D.) offers opportunities for research on evolutionary, developmental, and ecological factors relating to brain function and behavior Large outdoor and indoor habitats are available for comparative studies or reptiles, birds, and mammals living under semi-natural conditions. Th laboratories are equipped for neuroanatomical research, microelectrod recording, brain stimulation, psychological testing, and a computer system with high speed graphics capability for recording and processing electrophysiological and behavioral data. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior. Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, and ecology. The laboratory is beautifully located at the NIH Animal Center near Poolesville, Maryland, with open fields, a large pond for water fowl, and woodlands.

The DIVISION OF SPECIAL MENTAL HEALTH RESEARCH (R. J. Wyatt, M.D., Acting Director) located at Saint Elizabeths Hospital, (1) plans and conducts a program of intramural research on special mental health problems such as psychopharmacology, neuropharmacology, memory, and human behavior and (2) performs clinical evaluation and followup activities in connection with research patients.

The LABORATORY OF CLINICAL PSYCHOPHARMACOLOGY (Richard J. Wyatt, M.D., Chief; Senior Staff: J. C. Gillin, M.D., T. Reynolds, M.D., Lewellyn Bigelow, M.D., F. Karoum, Ph.D., and R. Stillman M.D.) uses biological techniques to study both specific and generalized systems operating in the normal human brain. Chemical, physiological, and psychological behavior of these normal systems is compared to putative abnormal ones in psychiatric patients. The comparisons of normal and abnormal behaviors lead to hypotheses as to cause and possible treatment. The principle behavioral abnormality studied is schizophrenia although presenile dementia, aging, and problems of drug abuse are also investigated. The laboratory operates three research wards consisting of about 12 beds each in which a variety of pharmacological, physiological, sleep, biochemical, and psychological studies are conducted on psychiatric patients and normal volunteers. The laboratory is equipped with physiological and chemical equipment including gas chromatography, mass spectrometry, as well as computer and animal facilities. Because of the diversity of approaches used, the laboratory seeks applicants who have both clinical and laboratory interests. For second year residents wanting credit for a third year of residency we have usually been able to make arrangements for credit with the university or hospital with which the resident spent his first two years.

The LABORATORY OF NEUROPHARMACOLOGY (Richard J. Wyatt, M.D., Acting Chief; Senior Staff: G. R. Siggins, Ph.D., F. F. Weight M.D.) conducts a multidisciplinary research program centered upon the identification of synaptic transmitter substances, and the mechanisms by which neuro-active and psycho-active drugs exhibit effects upon synaptic transmission. The approach is entirely at the cellular level, utilizing intracellular and extracellular electrophysiologic techniques, micromethods of drug administration including microelectrophoresis, and cytochemical studies with light, fluorescence, and electron microscopy. Specifically, studies are currently being carried out on: (1) the characterization and pharmacology of potential monoamine-containing neuronal pathways in the mammalian central nervous system; (2) the relation between pharmacological responsiveness and development of structurally specialized synapses; and (3) the cytologic and physiologic organization of sympathetic ganglia.

The Laboratory of Preclinical Pharmacology (E. Costa, M.D., Chief) conducts research in neurochemistry and neuropharmacology to elucidate control mechanisms involved in the clinical response of drugs affecting neuronal function. The laboratory is organized into four groups: (1) Group on High Pressure Liquid Chromatography (Senior Staff: J. Meek and T. Bohan); (2) The Section on Molecular Pharmacodynamics (E. Costa, M.D., Chief; Senior Staff: D. L. Cheney, Ph.D., D. M. Chuang, Ph.D., M. Gnegy, Ph.D., C. C. Mao, Ph.D., J. Schwartz, Ph.D., H-Y. T. Yang, Ph.D., and P. Uzunov, M.D., Ph.D.) conducts pharmacological studies on: (a) the dynamics of catecholamine and indolealkylamines in discrete brain nuclei using pulse labeling with 18_{02} and mass fragmentography to measure turnover rate of these putative neurotransmitters; (b) the dynamics of acetylcholine in discrete brain nuclei using pulse labeling with deuterated precursors and mass fragmentography to measure turnover rate of acetylcholine; (c) the regulation of the biosynthesis of the rate limiting enzymes that control the turnover of neurotransmitters; and (d) the regulation of cyclic nucleotide phosphodiesterase activity by endogenous proteic activators. (3) The Section on Biochemical Pharmacology (N. H. Neff, Ph.D., Chief; Senior Staff: H-Y. Yang, Ph.D.) conducts investigations directed at: (a) measuring turnover rates of regulatory enzymes of the dynamics of putative brain neurotransmitters; and (b) identifying and characterizing enzymes controlling the metabolism of endogenous polypeptides in the brain. (4) The Section on Neuroendocrinology (A. Guidotti, M.D., Chief) conducts studies concerning (a) the molecular mechanisms involved in the trans-synaptic induction of tyrosine hydroxylase; (b) the activation of cAMP dependent protein kinases in relation to the neuroendocrine control of pituitary and pineal glands; and (c) the role of cGMP and cAMP in the synaptic action of amino acids functioning as neurotransmitters.

National Institute of Neurological and Communicative Disorders and Stroke

Donald B. Tower, M.D., Ph.D., Director

General. The National Institute of Neurological and Communicative Disorders and Stroke conducts, fosters, and coordinates research on the causes, prevention, diagnosis, and treatment of neurological and sensory disorders and related fields, and administers a program of research and training grants and awards.

Throughout the Institute, opportunities also exist for clinical and professional education, including many scientific disciplines.

Intramural Research Program

Thomas N. Chase, M.D., Director
Donald B. Calne, M.D., Clinical Director

The Medical Neurology Branch (W. King Engel, M.D., Chief) has as its major function the application of basic research techniques to the investigation of clinical neurological problems. The Clinical Associate becomes acquainted with a majority of the neurological diseases with particular emphasis on the disorders of muscle, myasthenia gravis, lower motor neuron diseases, metabolic abnormalities of the central nervous system, and genetically determined disorders. He receives instruction in clinical neurology and the related clinical and basic sciences while developing an understanding of the various laboratory techniques which support the neurological investigation. During the first 12 months he is in a ward environment and is responsible for the care of patients on the Medical Neurology Service and the integration of related research. He covers the neurologic consultations to the other clinical services during 3 of those months. During the first year he is expected to learn to perform one of a variety of basic laboratory techniques (such as histochemistry, tissue culture, biochemistry, electron microscopy, immunology, autoradiography, or electromyography) as it applies to a clinical problem. The second year is spent in full-time work on that clinical research technique. Some Clinical Associates may stay a third year to continue their clinical research activities. The program is accredited for 1 year of residency training in neurology.

The Surgical Neurology Branch (Ayub K. Ommaya, M.D., F.R.C.S., Acting Chief) investigates problems in neural trauma, brain tumors, the surgical prophylaxis of strokes, and cerebrovascular disease management.

The Clinical Associate is required to study and has responsibility for the care of patients with brain tumors, strokes, and vascular malformations of the nervous system, and others with a variety of neurological disease. He receives practice and instruction in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating theater. He is also assigned to one of a number of laboratory projects designed to provide animal model correlation with the human disease under study. He is expected to learn and use new experimental techniques and work in collaboration with Senior Scientists.

The Branch of Clinical Neurosciences (Cosimo Ajmone Marsan, M.D., Chief) consists of two sections: Clinical Neurophysiology and Functional Neurosurgery. The Branch involves a relatively small, highly specialized patient population in addition to that referred from the entire Clinical Center for EEG examination. The position of Clinical Associate in Neurosurgery is for a 2- or 3-year appointment. Preference is given to persons with basic neurological or neurosurgical training. Appointments in neurophysiology are also for 2 or 3 years. Preference is given to people with some previous experience in the field of electrophysiology and a knowledge of neuroanatomy. Current research: experimental epilepsy, involuntary movements, thalamo-cortical relationship, nature of brain waves, microelectrode study of cortical neurons, etc.

The DEVELOPMENTAL AND METABOLIC NEUROLOGY BRANCH (Roscoe O. Brady, M.D., Chief; Anatole S. Dekaban, M.D., Associate Chief for Clinical Investigation). The branch is devoted to cross-disciplinary basic investigations and clinical studies of disorders of the nervous system. The research deals with (1) the pathological biochemistry, diagnosis, and therapy of inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, and Tay-Sachs disease; (2) functional abnormalities of the nervous system, including epilepsy; (3) heritable and acquired demyelinating conditions such as multiple sclerosis; and (4) the metabolism of complex lipids in tumorigenic virus-transformed cells.

The branch is comprised of the Section on Enzymology and Genetics (Dr. R. O. Brady, Head), the Section on Neurochemical Methodology (Dr. A. E. Gal, Head), and the Section on Clinical Investigations and Therapeutics (Dr. A. S. Dekaban, Head). The first two sections are primarily devoted to basic research; in- and outpatient study is included in the Section on Clinical Investigations and Therapeutics.

The INFECTIOUS DISEASES BRANCH (J. L. Sever, M.D., Ph.D., Chief) conducts studies of acute and chronic diseases and infections of the central nervous system. Both clinical and laboratory investigations are pursued in the areas of 1) neurogenetics, 2) immunochemistry and clinical investigations, 3) virology and bacteriology, 4) electron microscopy, and 5) experimental pathology. These studies will utilize genetic techniques and HLA-MLC tissue typing, new methods for cellular and humoral immune responses, virus serology tests, human volunteer and clinical trials, extensive virus isolation methods, electron microscopy as well as experimental studies with non-human primates. Current emphasis is on multiple sclerosis, Parkinson's disease, SSPE, Reye's syndrome, and perinatal infections which damage the developing fetus. New techniques are being used to detect acute and chronic infections of the central nervous system. Training is provided in the investigative areas listed above, and clinical experience with these investigations is available.

LABORATORY OF NEUROPHARMACOLOGY (Thomas N. Chase, M.D., Chief) conducts basic as well as clinically applied studies of central neurohumoral mechanisms and their relation to the pathogenesis of various disorders of nervous system function. Current research projects include (1) preclinical studies of the synthesis, metabolism, release, and receptor interactions of monoamines, γ-aminobutyric acid and other central neurotransmitters; (2) mechanisms of action of drugs which affect the nervous system; (3) clinical and biochemical studies of patients with disorders such as parkinsonism, epilepsy, and amyotrophic lateral sclerosis; and (4) clinical assessment of new therapeutic agents.

LABORATORY OF NEURO-OTOLARYNGOLOGY (Jorgen Fex, M.D., Ph.D., Chief). This laboratory is a new facility. The mammalian inner ear is being studied, using techniques of anatomy, biochemistry, and neurophysiology.

A project is underway to study inner ear mechanisms of synaptic excitation in the mammal. A second project concerns synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A major, long-term program of the laboratory is to solve problems concerning hereditary hearing disorders in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models. It is expected that experiments on cultures of the mouse hearing organ will be initiated.

Laboratory of Neurochemistry (R. Wayne Albers, Ph.D., Acting Chief) conducts research into the molecular events that underlie the normal functioning of the nervous system and the derangements which occur in neurological diseases. The Laboratory consists of three sections: the Section on Enzymes (Head, R. W. Albers), the Section on Neural Development and Regeneration (Acting Head, A. A. Zalewski), and the Section on Physiology and Metabolism (Head, E. G. Trams). The current investigations of the Laboratory employ a variety of disciplinary approaches and methodologies and encompass studies on isolated enzymes, neuronal cells in culture, and of neural metabolism in intact animals. Programs relate to the molecular mechanisms subserving the generation of cell membrane potentials, the structure of excitable membranes, neurotropic factors, neuronal regeneration and nucleotide metabolism, among others.

The Laboratory of Molecular Biology (Ernst Freese, Ph.D., Chief) examines the molecular mechanisms of biological processes that are affected in hereditary and viral diseases or in teratogenic effects.

In the Section on Molecular Virology (Dr. R. A. Lazzarini, Head) the control of cellular and viral RNA synthesis is studied in tissue cultures. In particular, the transcription and replication of the myxo- and paramyxoviruses is examined at the molecular level.

In the Section on Developmental Biology (Dr. Ernst Freese, Head) the transport of substrates through cellular membranes and other membrane-associated phenomena are studied in growing and differentiating bacteria and tissue cultures, as well as in isolated membrane vesicles. The inhibition of these reactions by lipophilic compounds, present in the human environment and partly known to have neurological effects, is analyzed. In addition, the section determines the biochemical reason why compounds accumulating in cacogenic mutants prevent normal development or produce hereditary diseases, and it endeavors to find means of avoiding this accumulation or preventing its effect. Bacterial systems, with their powerful genetic and biochemical possibilities, are compared with human tissue cultures.

The Laboratory of Neuropathology and Neuroanatomical Sciences (Igor Klatzo, M.D., Chief) recognizes scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomical sciences. Thus investigations on basic pathogenic mechanisms operative in various neuropathological conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system. Specific problems under current investigation are: cerebral ischemia, hypoxia, brain edema, role of the glia, development and pathology of myelin, control of carbohydrate metabolism, aspects of vascular permeability and transport mechanisms in the brain, mechanisms of neurohormonal regulation, localization of catecholamines, elucidation of some of the sensory and motor systems, investigation of neural membranes, junctional complexes, as well as the source and fate of synaptic vesicles. The main technical approaches include light and electron microscopy, freeze-fracturing, histochemistry, radioisotopic, biochemical and microchemical assays, and tissue culture. The laboratory is divided into seven sections:

(1) the Section on Functional Neuroanatomy (Thomas Reese, M.D., Head),

(2) the Section on Neurocytology (Milton Brightman, Ph.D., Head),

(3) the Section on Experimental Neuropathology, (Jan Cammermeyer, M.D., Head),

(4) the Section on Cerebral Vascular Pathology (Igor Klatzo, M.D., Head),

(5) the Section on Cellular Neuropathology (Henry Webster, M.D., Head),

(6) the Section on Cellular Neurochemistry (Janet Passonneau, Ph.D., Head), and

(7) the Section on Neurocytobiology (Maria Spatz, M.D., Head).

The LABORATORY OF NEUROPHYSIOLOGY (M. G. F. Fuortes, M.D., Chief) conducts research on basic properties of nerve cells and on the organization of the nervous system. The morphology of cells, synapses and subcellular structures is studied by means of optical and electron microscopy. Membrane properties of receptor cells and central neurons are investigated by electrophysiological methods. Work on receptor functions include kinetic studies aimed at determining the properties of the transduction processes. The properties of central neurons and synapses are studied in simple preparations derived from vertebrates and invertebrates. Electrical and chemical properties of cells in tissue culture are also being investigated.

The LABORATORY OF EXPERIMENTAL NEUROLOGY (William F. Caveness, M.D., Chief) includes the following activities: (1) the investigation of the delayed effects of high energy radiation to the whole brain of the Macaca mulatta according to clinical therapeutic regimens. The functional alterations are monitored with clinical examinations, funduscopic photography, and chemical analyses of cerebrospinal fluid at four week intervals following exposure. At eight week intervals, the brains are subjected to definitive histological examination at a collaborating facility, (2) the study of development and propagation of focal seizures in the developing brain of the monkey with the use of electrophysiological and regional blood flow techniques. Particular attention is directed to the subcortical nuclear masses.

One Research Associate position is available for 2 to 3 years. Previous experience in neuroanatomy or neuropharmacology is essential.

The LABORATORY OF NEURAL CONTROL (Robert E. Burke, M.D., Acting Chief) conducts fundamental research on the properties of mammalian nerve cells and on the organization of the mammalian central nervous system with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1) the central nervous system control of spinal cord motoneurons and the control exerted by these cells in turn on the muscle fibers innervated by them; 2) the organization of information processing systems in the spinal cord; and 3) the activity of central neurons and peripheral afferents during normal movement in intact animals. Such studies utilize both established and newly developed techniques for electrophysiological recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The Laboratory has facilities for development of specialized experimental equipment and novel electrode designs, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

The CENTRAL NERVOUS SYSTEM STUDIES LABORATORY (D. Carleton Gajdusek, M.D., Chief) is engaged in two studies: (1) complete medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior and learning; and (2) slow, latent, and temperate virus infections of the central nervous system, with particular attention to chronic degenerative neurological disease and basic virological and immunological studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie and mink encephalopathy) which form a new group of microorganisms tentatively called "viruses," although containing much smaller genetic information and possessing very different properties than any other group of viral agents. The biological and molecular characterization of these unconventional viruses is the major focus of the work. Aspects of learning and socialization in primitive disappearing cultures are documented using still and cinema photographic recording and sound recording. New methods of handling such data are developed.

Neurological Disorders Program

J. Kiffin Penry, M.D., Director

The goal of the Neurological Disorders Program is to plan and direct a program of grant and contract support for research and research training on neurological disorders to insure maximum utilization of available resources in attainment of Institute objectives; and to collaborate with intramural programs in the Institute and NIH-wide. The program is charged with the study of national priority diseases such as epilepsy, developmental disorders of children and adults, sclerosing and neuromuscular disorders, infectious diseases and tumors of the central nervous system, neuroendocrine studies, and learning, behavior and other sensory disorders. A number of the studies underway are collaborative studies which encompass the input of a number of outside institutions. The following programs are conducted by the Neurological Disorders Program of NINCDS.

The Epilepsy Branch, under J. Kiffin Penry, M.D., develops and coordinates organized and directed research programs on a multi-institutional geographic, or multidisciplinary basis; develops, conducts, and coordinates collaborative and directed research programs aimed at finding new methods of diagnosis, treatment, and prevention of convulsive disorders; synthesizes, screens, studies the pharmacology, and clinically evaluates antiepileptic drugs within its own facilities or supports these activities through extramural contracts or grants.

The Developmental Neurology Branch, under Joseph S. Drage, M.D., plans and implements a program of grant and contract supported research on the neurological basis of developmental disorders of children, including the areas of cerebral palsy, autism, mental retardation, learning and behavioral disorders, central nervous system birth defects, heritable muscle and neurological diseases, and minimal brain dysfunction; assesses need for research and research training in such areas; determines and recommends program priorities and funding levels for such areas; consults with professional and voluntary health organizations in identifying, developing, and implementing a research program focused on the neurological basis of developmental disorders of children; provides for the archival and retrieval system of the Collaborative Perinatal Project data and promotes the appropriate use of this national data resource commensurate with the goals and mission of the NINCDS.

The Neuroimmunology Branch (Dale E. McFarlin, M.D., Chief) has recently been established. This group is doing research in the following areas: (1) Characterization of the immune response to viral agents; in particular agents such as measles which cause chronic infection in patients with neurological diseases, and certain animal models are being studied. (2) Assessment of the immune response to membrane components of membranes in the peripheral and central nervous system. (3) Evaluation of immune function in patients with chronic neurological disorders of unknown etiology such as multiple sclerosis and parkinsonism which may be related to either an atypical infection of the nervous system or immunopathologic mechanisms. (4) Projects involving the clinical assessment of new therapeutic agents are planned in the future.

The Clinical Center

Mortimer B. Lipsett, M.D., Director
Griff T Ross, M.D., Ph.D., Deputy Director
Philippe V. Cardon, M.D., Associate Director

The Clinical Center appoints Clinical Associates for the Departments of Diagnostic Radiology, Blood Bank, Clinical Pathology, and Nuclear Medicine. Associates in Diagnostic Radiology are expected to have completed their residencies prior to entrance on duty.

The Blood Bank Department (Paul V. Holland, M.D., Chief) is accepting applications for Clinical Associates under the matching system. Applicants with at least 1 year of training post internship are preferred.

The Department supplies over 20,000 blood products annually for transfusion to patients with unique hematologic and immunologic problems. The use of blood components is stressed, with increasing emphasis on the use of frozen red cells in appropriate clinical situations. The medical staff consists of four full-time staff physicians and one clinical associate, as well as residents and medical students who are present for varying periods of training.

In addition to its service function, a significant proportion of Blood Bank activity is oriented toward clinical and basic research. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various Institutes. Current programs include investigations into hepatitis and the hepatitis B (Australia) antigen, the effects of biologic imcompatibilities on transfusion and transplantation, immunologic studies of drug-induced hemolytic anemias, and the use of computers in laboratory medicine.

The program offers training for the clinician in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. A close professional liaison is maintained with the Clinical Pathology Department through an active program of lectures, rounds, and seminars.

The Clinical Pathology Department (Ronald J. Elin, M.D., Ph.D., Chief) is accepting applications for Clinical Associates whose interests lie in specialized training and research in laboratory medicine. The department is organized into four main services: Clinical Chemistry, Hematology, Microbiology, and the Laboratory Computer Service. These areas are staffed by over 100 professional and technical personnel who form the operational base for the broad spectrum of laboratory diagnostic services called upon by the various Institutes for their intramural patient care programs. In addition, the professional staff of the department is engaged in collaborative and independent research in the areas relevant to laboratory medicine and the clinical diagnostic problems encountered at the Clinical Center. The department participates in the training of Residents in Clinical Pathology and interacts fully and on a professional consultative basis with the clinical programs at the National Institutes of Health.

Among the procedures and programs currently in operation in the department are automated assay systems for laboratory diagnosis, carbohydrate chromotography, amino-acid analysis, gas chromatography, radioimmunoassays, mineral metabolism studies, coagulation factor studies, certain host-defense mechanisms in infectious diseases, properties of bacterial endotoxins, diagnostic anaerobic bacteriology, and new approaches n the interface between computer assisted laboratory automation and data processing. These latter programs, in particular, are facilitated by direct access to the department's own computer facilities.

A close professional liaison is maintained with the Blood Bank Department.

A Clinical Associateship in any of the four services offers a broad experience in clinical and laboratory medicine. Each service carries on an active consultative role and participates extensively with many of the clinical services. In addition, each service provides supervised instruction in the functions of that area and opportunities are available for developmental investigation of the procedures of the clinical laboratory.

The DEPARTMENT OF DIAGNOSTIC RADIOLOGY (John L. Doppman, M.D., Chief).

Four Staff Radiologists are selected each year from among those applicants who have completed their residencies in Radiology or Diagnostic Roentgenology (Board certification not required). Such appointments are made for a period of 2 years with occasional opportunity for reappointment.

The department is well equipped to provide the routine and special diagnostic radiographic examinations needed by the 27,500 patients seen each year. The preselection of patients for admission to the NIH insures a challenging and stimulating gamut of diagnostic problems.

Twelve radiologists comprise the professional staff and an adequate supporting staff is provided.

Facilities are available for both collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

The DEPARTMENT OF NUCLEAR MEDICINE (Gerald S. Johnston, M.D., Chief). One Clinical Associate is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in Nuclear Medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved Internal Medicine, Radiology, or Clinical Pathology is recommended in order to meet the requirements for certification by the American Board of Nuclear Medicine.

The American Medical Association has approved the department for a 2-year residency training program in Nuclear Medicine. Qualifications for trainees include at least 2 years of prior training in Radiology, Pathology, or Internal Medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital and the Maryland University Hospital.

The department consists of four sections: Diagnostic Nuclear Medicine Section, Whole Body Counter Section, Radiopharmacy Section, and Applied Physics Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various Institutes working within the Clinical Center. Dual probe rectilinear scanners and gamma cameras are the basic imaging devices. Dedicated computers supported by NIH computer experts from DCRT are located within the section. The Applied Physics Section and DCRT personnel work cooperatively in the development of new diagnostic techniques. The Whole Body Counter Section works closely with the Diagnostic Section and the Radiation Safety Office. It operates three whole body counters and provides a consultation service to all the Institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staffs of the Diagnostic and Whole Body Counter Sections consist of seven physicians, a radiobiologist, a nuclear physicist, an equipment specialist, seven nuclear medical technicians, and three clerks. Departmental professionals are encouraged to interact with members of the various Institutes in order to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases.

The Radiopharmacy Section employs three full-time radiopharmacists, a technician, and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by Diagnostic Nuclear Medicine. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

PART FOUR

Academic Programs Available to Associates

AMONG the academic programs open to an NIH Associate are: Evening courses provided by the Foundation for Advanced Education in the Sciences, Inc.; formal seminars under the direction of NIH staff; Combined Clinical Staff Conferences; formal lectures; symposia; and an annual scientific equipment exhibit. The "N.I.H. Calendar of Events" lists 25 to 30 programs each week. Other events of interest are held at universities and other institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. Established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science, the Foundation is a non-Federal independent organization as defined by the Government Employees Training Act; however, its tuition and other fees can be paid by a Federal employer. Courses are offered in two semesters, fall and spring; courses are offered at the undergraduate and graduate levels under the programs of its several departments of instruction: Behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. Further inquiries regarding The Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education n the Sciences, Inc., National Institutes of Health, Bethesda, Md. 20014.

Seminars

An NIH Program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent nvestigators, and gives them the additional opportunity to master selected opics not adequately covered during college or graduate schooling. These exercises are an integral part of the Associate Program and are geared specifically in that direction. The program accommodates Research, Staff, and Clinical Associates and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics; cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of an expert in the field. In preparation for these, the Associate does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate Institutes engaged in clinical research, the Clinical Center sponsors at least one monthly Combined Clinical Staff Conference for 8 months of the year. Each conference is conducted by one of the Institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff, and serve to keep individual investigators abreast of current emphasis in all clinical research.

Several formal lectures are presented annually. The National Institutes of Health Lecture Series was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the Scientific Directors of the Institutes. The R. E. Dyer Lectureship was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942–50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science; it is administered by NIH.

The Jules Freund lecture series was established in 1961 and is presented annually in honor of the first Chief of the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases.

The G. Burroughs Mider Lectureship was established in 1968 by the Scientific Directors to honor Dr. Mider for his distinguished service to NIH. On advice of the Scientific Directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Equipment Exhibit: Symposia

The NIH Research Equipment Exhibit was established in 1951 to acquaint scientists with the most modern research tools and to give them an opportunity to discuss equipment problems with representatives of industry. In 1954, a Symposium on Recent Developments in Research Methods and Instrumentation was added, offering a balanced presentation by specialists in many areas of biomedical research. The two annual events combined to provide a convenient setting for the exchange of information between research investigators and manufacturers of scientific equipment.

The NIH International Symposium on Biomedical Research was established in 1963 to emphasize the mutuality of interest of NIH and the international scientific community, particularly with the extension of NIH programs overseas.

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Naval Medical Center, offer exceptional opportunities. Some Associates find the time to pursue a certain amount of formal education at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located in the Clinical Center) provides a central facility for the scientific, medical, administrative and supportive staff engaged in the NIH research program. As a self-service, open-stack library, it contains a collection of 110,000 volumes and receives annually 5,000 monographs and 3,000 foreign and domestic journals. In addition to the usual library services, the NIH Library provides on-line access to NLM's medical literature data banks, advisory services for literature needs, and a translating service.

The National Library of Medicine is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 1 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service.

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1978

February 15	Deadline for receipt of completed NIH Associate applications
April 17-28	Interview period
May 16-31	Notification to all candidates

FOREWORD

The National Institutes of Health is the primary biomedical research arm of the Federal Government and is dedicated to the broad missions of improving health and curing disease. To do this, it supports biomedical research and training throughout the country and conducts its own research programs.

The NIH intramural research facilities are located on a 306-acre campus in Bethesda, Maryland. The Clinical Center, the hospital for clinical investigations, has 541 beds and more than 1,000 laboratories. The 4,500 patients admitted during the past year participated in many of the 1,400 research projects. The professional staff at NIH comprises 2,000 investigators with doctoral degrees, over half of whom are physicians.

The association with scientists and physicians of international repute fosters the spirit of scientific inquiry and medical research. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Associate Program at the NIH.

MORTIMER B. LIPSETT, M.D.
Director
The Clinical Center

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PART ONE

General Description of Associateships and Other Opportunities

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Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists who receive appointments as Clinical, Research, and Staff Associates at the National Institutes of Health. These positions encompass most of the medical specialties as well as the basic science disciplines.

Appointments to the Associate Training Program are based on intellectual attainment and demonstrated research interest and ability. An individual's background in research is often decisive in making selections but sometimes clinical expertise in a specialty is the main criterion. Selections are made through a matching process, explained in Part Two.

Each Associate participates in a research program under the direction of a preceptor. Preceptors help Associates to enrich their experience in research and in other ways. The research responsibilities and latitude given to Associates depend on their capacities, interests, and initiative.

Teaching sessions designed to complement Associateships are held regularly. In addition, postgraduate instruction is available through evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. (See Part Four). Associates in many program areas are expected to take advantage of academic opportunities on the NIH campus.

A candidate may enter the Associate Program as a member of the Public Health Service Commissioned Corps, or as a nontenured civilian employee.

All applicants are carefully considered. NIH welcomes applications from women and members of all minority groups.

The Clinical Associate

The Clinical Associate participates in both clinical and laboratory research. Institute programs differ in the proportion of time devoted to laboratory and clinical responsibilities.

Clinical activities are under the immediate supervision of senior investigators, and include rounds, conferences, and other instructive exercises. The proximity between the patients and collaborating scientists from many biological disciplines has created an unusual environment for clinical investigation. The environment is also enriched by the presence of medical students from all parts of the country with whom Clinical Associates have close contact and share responsibility for patient care.

Limited residency and/or subspecialty credit for Board certification may be accorded Associates in several of the training programs.

The Dental Clinical Associate

Like his physician Clinical Associate counterpart, the Dental Clinical Associate may participate in laboratory and clinical research, and at the same time enhance his professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the Associateship, full opportunity is provided for: (1) familiarity with all ongoing research programs relevant to dentistry; (2) affiliation with one or more preceptors for participation in a mutually acceptable area of investigation; and (3) extension of scientific background through rounds, conferences, seminars, and formalized course work.

The Research Associate

The Research Associate devotes most of his time to laboratory research in a biomedical science. His preceptor is responsible for training him in research methodology and design, and for guiding him in the conduct of specific research undertakings and in the interpretation of results. A goal is to select research problems which will enable the Associate to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The Pharmacology Research Associate

Sponsored by the National Institute of General Medical Sciences, Pharmacology Research Associates spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those who have made a commitment to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

The Staff Associate

The Staff Associate position provides opportunities for those highly qualified candidates who could contribute significantly to research in areas which are not specifically designated in the Research or Clinical Associate categories. The Staff Associate may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he works. Research experience may be supplemented by formal evening study courses, as well as by attendance at lectures by guest speakers and a variety of regularly scheduled seminars.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to students from any of the nation's medical schools. For 1978-79, the staffs of several

Institutes are collaborating to supply an in-depth exposure to ten clinical subspecialties: Computers in Clinical Medicine, Endocrinology and Metabolism, Gastroenterology, Genetics, Immunology, Infectious Diseases, Nuclear Medicine, Oncology-Hematology, Psychopharmacology, and Surgical Oncology.

The essence of this educational experience is a close association between the student, clinical associates, and physician-scientists in several of the Institutes.

Students have patients assigned to them for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with particular interests in fields other than those listed above are sometimes arranged through communications between an NIH staff member and a faculty sponsor of the student.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Associate Director for Medical Education
The Clinical Center
National Institutes of Health
Bethesda, Md. 20014

Residency Programs

Fully approved residency programs are offered in anatomical pathology, clinical pathology, and combined clinical and anatomical pathology.

In 1974 the American Medical Association established requirements for a residency in blood banking. An approved blood bank residency program is now offered to interested applicants.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Ronald J. Elin, M.D., Ph.D.
Chief, Clinical Pathology Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

Louis B. Thomas, M.D.
Chief, Laboratory of Pathology
National Cancer Institute
National Institutes of Health
Bethesda, Md. 20014

Paul V. Holland, M.D.
Chief, Blood Bank Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

On the basis of agreements between program chiefs and appropriate American Specialty Boards, Clinical Associates in dermatology, psychiatry, and neurology may receive credit for 1 year each, and 2 years in nuclear medicine.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as Associates, but as Staff Physicians. Initial appointments are temporary and usually for 2 years, but some Staff Physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in ongoing research.

PART TWO

Applying for an Associateship

About 100 Clinical Associates and 50 Research and Staff Associates are appointed annually. Associates may be employed through the Commissioned Corps of the Public Health Service or through a Civil Service mechanism. Of course, if applying through Civil Service, it is not necessary to submit the PHS commissioning forms.

Minimum eligibility requirements for most Associateships is completion of two years of postdoctoral training before entrance on duty. Application should be made between one and two years before desired date of appointment.

To be considered for a Clinical, Research, or Staff Associate appointment, the following forms must be received in the NIH Associate Office, National Institutes of Health, Bethesda, Md. 20014:

- Information Record for Clinical, Research, and Staff Associate Positions
- Program Area Selection Check List
- NIH Associate Information and Status Record
- Interview Information Record
- Application for Appointment as a Commissioned Officer in the Public Health Service (2 copies)
- Fingerprint Chart (fingerprints may be obtained at PHS facilities, local police, or post office)
- Data for Nonsensitive or Noncritical Position.

The applicant is responsible for requesting the following materials be sent directly to the NIH Associates Office.

- Three sets of references from professional persons whom the candidate has listed on the NIH information sheet. Each set consists of: (1) Request for Confidential Evaluation of Applicant for Appointment as an NIH Associate; and (2) Reference Request (Commissioned Corps)
- Two copies of all college and medical or dental school transcripts (showing class standing, if available).

Public Health Service Commissioned Corps

The Commissioned Corps is a uniformed service similar in many respects to the Army, Navy, and Air Force. It is a uniquely "all officer" Corps, comprised largely of professionals in medical and health related fields.

Pay, allowances, and other benefits are comparable to those of officers of the Armed Forces. Benefits include medical care for officers and dependents; tax-free allowances for quarters and subsistence; commissary, post exchange, and officers' club privileges; and 30 days annual leave.

While most career PHS officers are eligible for the variable incentive pay (VIP) "bonus," VIP is not an immediate incentive to prospective Associates. Officers serving in their first 2 years as Associates, and officers performing obligated service incurred through participation in Senior COSTEP Program are *not* eligible for VIP.

For those considering longer periods of service or careers in the PHS, the advantages of subsequent VIP, and of noncontributory retirement and survivor benefit plans are substantial.

To be eligible for the Commissioned Corps for participation as an NIH Associate, a candidate must meet the following requirements:

1. Be a United States citizen.
2. Meet the medical fitness standards.
3. Be a graduate of an accredited medical or dental school.
4. Satisfactorily complete an internship approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)

Early Commissioning Program for Medical Students (PHS Senior COSTEP Program)

Qualified candidates who will be in their senior or last year of medical school during academic year 1978–79 may apply for an Associateship through this program. It should be noted, however, that not all NIH programs consider Senior COSTEP applicants.

Successful candidates are appointed and placed on active duty as commissioned officers in the Reserve Corps of the Public Health Service during their senior or final year. They receive full pay and allowances as Junior Assistant Health Service Officers (equivalent to Navy Ensign), plus payment of tuition, fees, and other related expenses. In return for this financial support, they are obligated to serve on active duty as medical officers with the PHS for a minimum of 2 years.

Applications cannot be considered from members of another uniformed service or anyone having a service commitment upon graduation other than to the Public Health Service.

Civilian Staff Fellowships

As an alternative to the Commissioned Corps, Associates may be appointed as Staff Fellows. This is a temporary Civil Service appointment. Salaries are similar to those of Commissioned Corps officers who do not receive the variable incentive pay "bonus." Medical fitness standards are less stringent, and noncitizens of the United States who are eligible for naturalization within 4 years may be appointed. Usually, Fellows earn slightly less annual leave. Comparative advantages of retirement plans and fringe benefits depend largely on individual circumstances and preferences.

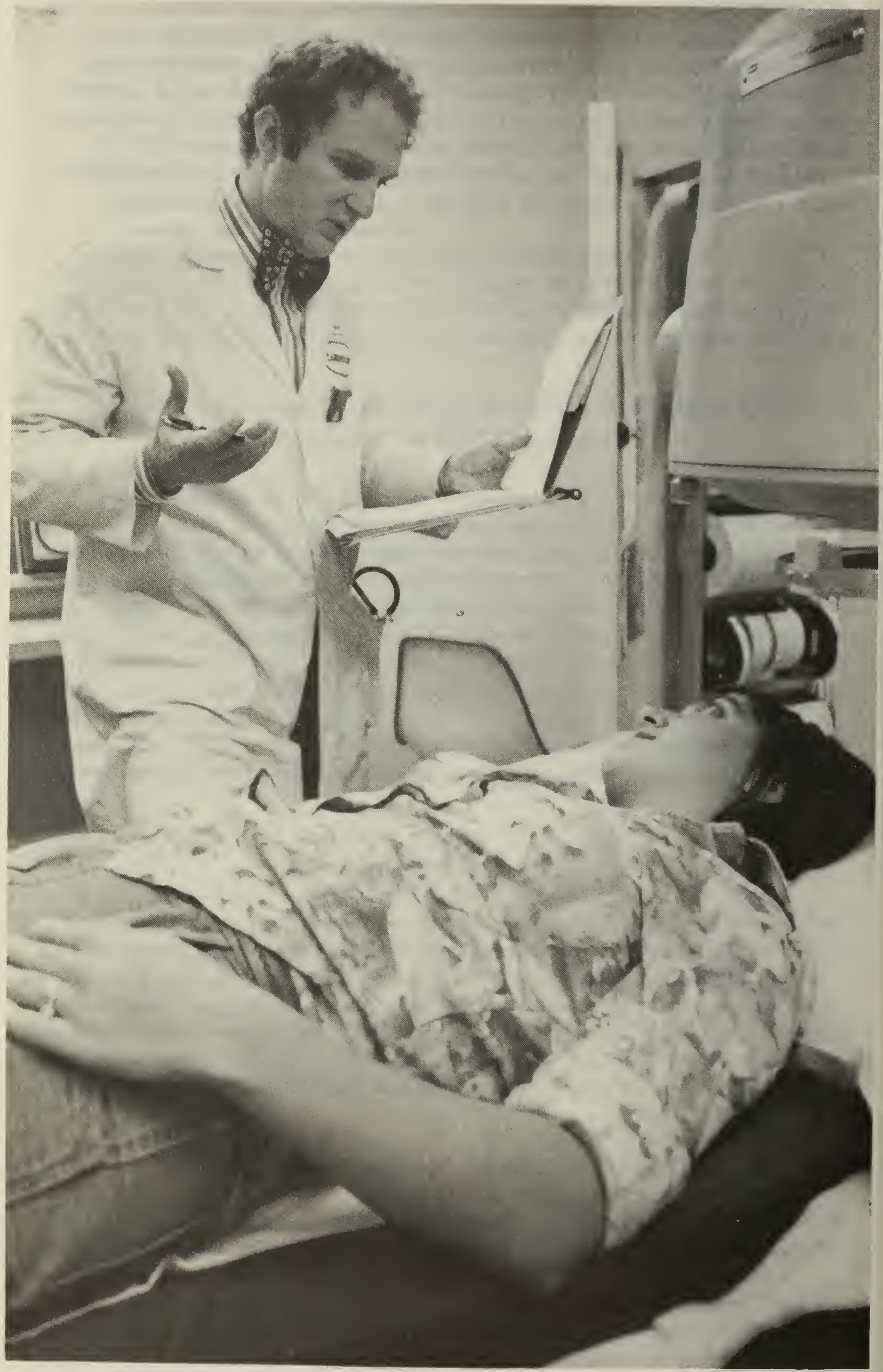
Method of Selection—Matching Program

Selections for the Clinical, Research, and Staff Associate appointments are made through a matching process in which the candidate's preferences are matched with the Institute preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Check List." After reading Part Three of this catalog, candidate should check off on these sheets the areas in which candidate is interested. There is no limit to the number of interest areas which may be checked; although the candidate may have preferences among the areas checked, they should not be stated at this time. The application will be sent to all laboratories and branches which the candidate checks.

After thorough review of all applications by the Institutes, a limited number of candidates will be selected for personal interviews. NIH will pay air fare of those selected for interviews who elect to apply for Staff Fellow (civilian) appointment.

The NIH Associate office will set up the interviews and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.



PART THREE

Program Areas for Which Candidates May Apply

Each of the major NIH components has prepared a description of its program areas for which Associates may seek appointment. Due to diversity of the operations and programs within these major components, the descriptions do not follow a pattern. However, all of these descriptions are meant to anticipate the questions which applicants may have in selecting the program areas for which they wish to be considered. It should be noted that a candidate is not limited as to the number or kinds of positions for which he may apply.

National Cancer Institute

Guy R. Newell, M.D., Acting Director
Vincent T. DeVita, Jr., M.D., Clinical Director

Laboratories and Branches

Director, Division of Cancer Biology and Diagnosis, Alan S. Rabson, M.D.
    Associate Director for Program Planning, Irvin C. Plough, M.D.
        Chief, Laboratory of Biochemistry, Robert F. Goldberger, M.D.
        Chief, Laboratory of Cell Biology, Lloyd W. Law, Ph.D.
        Chief, Laboratory of Immunobiology, Herbert J. Rapp, Sc.D.
        Chief, Laboratory of Immunodiagnosis, Ronald B. Herberman, M.D.
        Chief, Laboratory of Molecular Biology, Ira H. Pastan, M.D.
        Chief, Laboratory of Pathology, Louis B. Thomas, M.D.
        Chief, Laboratory of Pathophysiology, Pietro M. Gullino, M.D.
        Acting Chief, Laboratory of Theoretical Biology, Mones Berman, Ph.D.
        Chief, Dermatology Branch, Marvin A. Lutzner, M.D.
        Chief, Immunology Branch, William D. Terry, M.D.
        Chief, Metabolism Branch, Thomas A. Waldmann, M.D.

Director, Division of Cancer Treatment, Vincent T. DeVita, Jr., M.D.
        Deputy Director, Saul Schepartz, Ph.D.
        Clinical Director, Vincent T. DeVita, Jr., M.D.
        Deputy Clinical Director, John L. Ziegler, M.D.

    Clinical Oncology Program, John L. Ziegler, M.D.
        Chief, Clinical Pharmacology Branch, Bruce A. Chabner, M.D.
        Chief, Medicine Branch, Robert C. Young, M.D.
        Chief, NCI-VA Medical Oncology Branch, John D. Minna, M.D.
        Chief, Pedatric Oncology Branch, Arthur S. Levine, M.D.

Chief, Radiation Oncology Branch, Ralph E. Johnson, M.D.
Chief, Surgery Branch, Steven A. Rosenberg, M.D.

Cancer Therapy Evaluation Program, Franco Muggia, M.D.
Chief, Combined Modality Branch, Franco Muggia, M.D.
Chief, Investigational Drug Branch, Vincent H. Bono, M.D.

Special Assistant, Clinical Investigations Branch, Hugh Davis, M.D.

Developmental Therapeutics Program, Vincent T. Oliverio, Ph.D.
Chief, Laboratory of Chemical Pharmacology, Richard A. Adamson, Ph.D.
Chief, Laboratory of Medicinal Chemistry and Biology, David G. Johns, Ph.D.
Chief, Laboratory of Molecular Pharmacology, Kurt W. Kohn, M.D., Ph.D.
Chief, Laboratory of Toxicology, Anthony M. Guarino, Ph.D.
Chief, Laboratory of Tumor Cell Biology, Robert C. Gallo, M.D.
Chief, Drug Evaluation Branch, John M. Venditti, Ph.D.
Chief, Drug Synthesis & Chemistry Branch, Harry B. Wood, Ph.D.
Chief, Pharmaceutical Resources Branch, Mr. Paul J. Davignon
Chief, Natural Products Branch, John D. Douros, Ph.D.

Baltimore Cancer Research Center, Michael D. Walker, M.D.
Chief, Clinical Oncology Branch, Peter H. Wiernik, M.D.
Chief, Laboratory of Clinical Biochemistry, Nicholas R. Bachur, M.D., Ph.D.
Chief, Laboratory of Molecular Biology, Carl C. Levy, Ph.D.

Division of Cancer Biology and Diagnosis

A broad range of research is carried out in both basic laboratories and clinical branches under the general direction of Dr. Alan S. Rabson.

The LABORATORY OF BIOCHEMISTRY consists of five sections. The CELLULAR REGULATION SECTION is concerned with the molecular mechanisms by which steroid hormones regulate specific gene expression in eukaryotes. The system under investigation is egg yolk phosphoprotein synthesis in the liver of the rooster after treatment with estrogen. This system has the advantages of a hormonal response that is highly specific and of great magnitude in a tissue capable of a wide diversity of genetic expression. The approach involves studies with purified components *in vitro* as well as with cultured cells and whole animals.

The NUCLEIC ACID ENZYMOLOGY SECTION is concerned with the study of nucleic acid metabolism and structure. Systems under study include the structure and origin of defective Simian Virus 40 DNA containing host DNA sequences; the organization of eukaryotic chromosomal DNA; bacterial polynucleotide phosphorylase; cyclic AMP metabolism; the role of histone 1 in chromatin structure. Emphasis is on reaction mechanisms as elucidated by structural studies. A variety of modern techniques of nucleic acid and protein chemistry are employed.

The BIOCHEMISTRY OF GENE EXPRESSION SECTION studies control of gene expression in eukaryotic cells and its application to clinical medicine. The effects of steroid hormones on enzyme induction both in cultured cells and cell hybrids are investigated, along with studies on steroid receptors in human leukemia and breast cancer. Techniques of cell culture, cell fusion, chromosome banding, cell-free protein synthesis, and affinity chromatography are among those utilized.

The BIOSYNTHESIS SECTION currently conducts research on the regulation of collagen biosynthesis, the molecular properties and function of eukaryotic DNA polymerases, the transcription of covalently linked host and viral (SV40) genetic information, and the regulation of cell surface configuration (using correlated electron microscopic and metabolic studies).

The PROTEIN CHEMISTRY SECTION is investigating biochemical changes accompanying the maturation of granulocytes in bone marrow, interactions between cells involved in the immune response, and the transfer of genetic information through the cellular uptake of isolated chromosomes. Tissue culture, protein fractionation, cell separation and radioisotopic procedures are employed.

Personnel of the LABORATORY OF CELL BIOLOGY have diverse interests focusing upon the study of transformation of a normal cell to a neoplastic cell. Techniques from the fields of virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization, and electron microscopy are used. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells (principally plasma cells), role of cell membranes in regulating differentiation and growth, identification and study of tumor antigens and of the specific immune reactions initiated, solubilization and purification of transplantation and tumor antigens, influence of somatic cell hybridization on expression of genetically determined events, and ultrastructural analysis and molecular biology of viral oncogenesis.

The LABORATORY OF IMMUNOBIOLOGY plans, develops, and conducts a research program aimed at elucidation of the role of cellular and humoral immune responses in the process of carcinogenesis, its inhibition, and the prevention of cancer growth and spread; biochemical and immunobiological characterization and elucidation of the structure of antigens derived from normal and malignant cells; the acquisition of detailed knowledge of the molecular and cellular events required for cell damage by antibodies and complement, by lymphocytes and macrophages, and by a combination of these humoral and cellular factors; and characterization of the pathologic effects of malignancy on the immune system. The Laboratory of Immunobiology consists of the following three sections:

The CELLULAR IMMUNITY SECTION conducts studies on lymphocytes, macrophages and other cells that participate in immunologic reactions; elucidates the mechanisms of cell-mediated cytotoxic reactions; and develops methods that promote cell-mediated destruction of tumor cells *in vitro* and *in vivo.*

The HUMORAL IMMUNITY SECTION conducts studies on the immunochemistry of antibodies, antigens and the components of complement; elucidates the mechanisms of cytotoxic reactions mediated by antibodies and complement; and develops and applies immunochemical tools to the detection and enumeration of normal and malignant antigens.

The IMMUNOPATHOLOGY SECTION conducts studies on the interactions of tumor cells and their products with the immune system; characterizes host cells responsible for lymphokine production, chemotaxis, and inflammation at sites of interaction with tumor cells; and studies *in vivo* and *in vitro* methods to correct the pathologic consequences of these interactions.

The LABORATORY OF IMMUNODIAGNOSIS conducts studies on the nature of tumor-associated antigens and other cell surface antigens on tumor cells and on the immune response to these antigens. The antigens in several tumor systems, both in animals and in man, are being studied, particularly in regard to their role in host resistance against tumor growth and their possible diagnostic applications. The cell-mediated and humoral immune responses to a variety of experimental and human tumors are being extensively studied. The assays for cellular immunity include radioisotopic and visual cytotoxicity assays, lymphocyte stimulation, migration inhibition, and skin tests for delayed hypersensitivity. The interrelationships among these assays and the usefulness of each for the diagnosis of cancer and for monitoring of tumor-bearing individuals are being investigated.

The program offers the opportunity to perform research in experimental tumor systems and/or to perform immunologic investigations on patients with cancer.

The LABORATORY OF MOLECULAR BIOLOGY investigates cell behavior, gene function and other regulatory mechanisms in animal and bacterial cells. Particular attention is given to the identification and isolation of regulatory molecules and to studies on the mechanism of action of these substances.

Cells transformed by oncogenic viruses as well as physical and chemical agents have alterations in cell shape, adhesiveness, motility, surface structure, and growth control. Transformed cells are employed to investigate the nature of molecules that control these phenomena. Special attention is now focused on two molecules that have a role in regulation of cell behavior and are often decreased in transformation. These are cyclic AMP and CSP; the latter is a large molecular weight cell surface protein. The regulation of the synthesis of this protein in normal cells and the mechanisms causing its reduced synthesis in transformed cells is under study. Mutants defective in adhesion, motility and growth control are isolated and employed for biochemical analysis, with particular attention to proteins associated with the plasma membrane and to contractile proteins. Other efforts are directed towards the elucidation of the viral gene products responsible for the initiation of transformation. The mammary tumor system in mice is under study with emphasis given to elucidating the morphologic and biochemical nature of the virus particle, and the identifying various lines of the virus. Regulation of oncornaviral expression in mammalian cells is studied using cell hybridization and chromosome segregation to induce viral replication.

Factors regulating the organization of subcellular organelles in cells, their position, number and turnover rates, and how they cooperate in cell function are under investigation. Processes such as cell growth, macropinocytosis, exocytosis, and transport of proteins within cells are of particular interest. Finally, investigations are being carried out on how cells interact in organ growth and function.

The regulation of prokaryotic gene expression is studied using cell-free systems containing purified proteins and specific bacterial and viral genes. Mutants defective in initiation and termination of transcription are isolated and employed to detect new regulatory compounds or to elucidate regulatory mechanisms. The nucleotide sequence of genetic regulatory regions is under intensive study.

Other efforts are directed towards investigating the molecular basis of genetic recombination. The studies employ the bacteriophage λ and its host, *E. coli*. Mutants defective in recombination are isolated and the nature of their defects analyzed by both genetic and biochemical methods. A biochemical and genetic analysis of DNA replication in *E. coli* is being performed. This study uses a variety of DNA phages and *E. coli* DNA replication mutants.

The LABORATORY OF PATHOLOGY of the National Cancer Institute offers a 2- to 4-year training program for residents in pathologic anatomy in the Clinical Center, National Institutes of Health, Bethesda, Maryland. The program, which is fully approved for Board certification, provides well supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. Opportunity is provided for learning many research techniques, particularly electron microscopy, fluorescence microscopy, tissue culture, histochemistry, autoradiography, and cytogenetics. Individual or collaborative participation in clinical or laboratory research projects by the residents and selected Research Fellows and Visiting Scientists is encouraged.

In addition to the autopsy, surgical pathology, and cytodiagnostic services, the laboratory also carries on a broad research program in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

Laboratory of Pathophysiology. The Section on Cellular and Molecular Physiology studies the biochemical mechanisms which control the early stages of cell growth induction in normal and neoplastic human cells. Emphasis is on the mechanisms which maintain physiologically resting cells in the non-growing condition and the early biochemical modifications which occur on growth stimulation. Current studies include characterization of translational controls in resting human lymphocytes, examination of facets of messenger RNA metabolism which are unique to physiologically resting cells, and studies of the regulation of the production of specific proteins whose synthesis is related to the onset of lymphocyte growth.

The Section on Cell Cycle Regulation is concerned with the characterization of biological events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the synthesis of oligo-(ADP-ribose), the activity of the enzyme complex synthesizing the oligomer, and the effect of a change in its concentration on the cell cycle.

The Section on Membrane Biology is devoted to the study of the structure, dynamics and function of biological membranes through transmission and scanning electron microscopy of freeze-fractured, freeze-etched and immunochemically labeled plasma membranes.

The Section on Nucleic Acids is studying the differences between nuclear and cytoplasmic DNA in an effort to characterize the chemical and physiological roles of DNA in mitochondria, melanin, and zymogen granules.

The Section on Energy Metabolism is concerned with the physiological and behavioral control of food and water intake and its relation to cancer cachexia.

The Section on Radiation Biology is involved in the use of radiation to destroy bone marrow and to study the laws governing marrow transplantation from donors. The effects of ionizing and UV radiation on nucleic acids and proteins are also being studied.

Finally, a group of projects concerning the process of mammary tumor regression, the role of hormonal deprivation of the host on cell survival, and the effect of cAMP on the initiation and progression of tumor regression, is carried on in collaboration with the Office of the Chief.

The Laboratory of Theoretical Biology is concerned with the formulation of theories of structure, function, and dynamics of biological systems and with the development of mathematical and computational techniques for the analysis of those systems. Several areas are of particular interest: (1) formal models for the kinetics of metabolites, therapeutic agents, and hormonal regulation; (2) membrane structure and function, including transport through artificial lipid bilayer membranes, interaction of lipid vesicles with cells, and mobility of cell surface components; (3) configurations and properties of polypeptides and other macromolecules; (4) immune response systems and surface receptors. Although the work is predominantly theoretical, experimental studies related to these problems are carried out within the laboratory and in collaboration with others.

The DERMATOLOGY BRANCH studies growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic and neoplastic states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; T-cell leukemias (Sezary syndrome and mycosis fungoides); and physiology of lymphoreticular cells and lymphokine formation. Also studied are experimental allergic contact dermatitis in man; scanning and transmission of the ultrastructure of normal and diseased skin and other tissues; scanning microscopy of the surface structure of cells in relation to the mitotic cycle and motility; genodermatoses; biochemical and ultrastructural aspects of melanogenesis in normal and melanoma tissue; biochemistry of keratinization; xeroderma pigmentosum—an inherited disease of sun sensitivity and multiple cutaneous cancers with abnormal DNA repair (complementation, mutagenesis and carcinogenesis); chemical and ultrastructural effects of Vitamin A on skin; the oncogenic potential of tumor viruses; the development of therapy of epithelial cancers, skin lymphomas, and keratinizing diseases of the skin.

The Branch is staffed by dermatologists, virologists, biochemists, morphologists, and immunologists active in the training of clinical and basic researchers. One year's credit towards Board certification in dermatology can be offered for time spent in the two-year clinical associateship program. Clinical Associates sometimes remain for a third and/or fourth year to complete research projects.

In the IMMUNOLOGY BRANCH, clinical and basic science approaches are combined in the study of immune responses to normal and malignant cell surface antigens. Fundamental investigations stress mechanisms of normal and disordered immune responses and modes of specifically modifying those responses. Immunochemical, biochemical, serologic, immunogenetic, and tissue culture techniques are applied to research on the structure and function of antibodies and cell surface receptors and the genetic control of immune responses. A variety of animal models are used in the study and characterization of histocompatability antigens, differentiation antigens, tumor specific antigens, and cell surface antigens of possible importance in cellular cooperation. Clinical interests include immunotherapy of malignant disease, transplantation immunology and *in vitro* correlates of immunity in disease states and during therapy.

The METABOLISM BRANCH has two major areas of clinical research, the first in clinical immunology and the second in clinical endocrinology and metabolism. The clinical and laboratory programs in immunology cover a broad range of immunological problems, especially as they involve immunodeficiency states in man associated with a high incidence of malignancy. The studies are concerned with the nature of the abnormalities of circulating and cellular immune responses in animal models and in patients with such disorders as agammaglobulinemia, the Wiskott-Aldrich syndrome, ataxia telangiectasia, multiple myeloma, chronic lymphocytic leukemia, intestinal lymphangiectasia, gluten-sensitive enteropathy and autoimmune diseases. Special attention is given to the role of abnormalities of suppressor cells in the pathogenesis of immunodeficiency, the role of macrophages in antigen processing and recognition, the factors controlling the differentiation of lymphoid cells, cell-surface membrane markers of lymphoid cells, the function of effector or killer cells and the relationship between human disease, and the immune response and histocompatability genes.

The second area of emphasis, clinical endocrinology and metabolism, involves the study of metabolic derangements of the homeostatic control mechanisms with special emphasis on the study of porphyrin metabolism, collagen metabolism, and hormonal control of growth. Patients with derangements of porphyrin metabolic pathways are studied in investigations of the factors regulating porphyrin biosynthesis. The regulation of the enzymes of pyrroline and collagen metabolism is studied in patients with genetic and acquired defects of collagen and bone metabolism. The mode of action of growth hormone and somatomedin in the biochemical events accompanying normal and disordered growth is being investigated.

The candidates for Clinical Associates in the Metabolism Branch ultimately apply for a position with a specific investigator on a program either in the immunological or endocrinological and metabolic areas of the Branch. During these two years the Clinical Associate will be involved in both laboratory and clinical investigations as well as clinical care of patients with illnesses related to his own research interests and those of his Senior Investigator. The goal of the training program is to provide the Associate experience in the techniques of clinical research as well as in either of the clinical superspecialty areas of immunology and allergy or endocrinology and metabolism.

Division of Cancer Treatment

An intensive program of laboratory research and clinical investigation concerned with the therapy of cancer is under the direction of Dr. Vincent T. DeVita, Jr. Emphasis is placed on combinations of drugs with other modalities of therapy including surgery, radiation, and immunotherapy.

The CANCER THERAPY EVALUATION PROGRAM is involved in monitoring clinical trials with investigational and known antineoplastic treatment modalities. The scope of the program has evolved from broad drug trials with investigational chemotherapeutic agents to disease-oriented approaches including incorporation of effective drug combinations during early stages of disease and testing of new modalities, such as immunotherapy, in combination with surgery, radiotherapy, and chemotherapy in specific diseases that were until now considered untreatable. With the new responsibility for coordinating activities in the cooperative oncology groups, the program is setting up meetings with representatives from all interested groups and institutions throughout the nation. Evaluation of effectiveness of types and methods of cancer therapy, and dissemination and exchange of information on clinical trials are also important aspects of the program.

The CLINICAL INVESTIGATIONS BRANCH is responsible for monitoring the activities of the cooperative oncology groups, including critical review of protocols and updating of information on clinical trials within and outside the group programs. The Branch serves as liaison between the National Cancer Institute and group investigators throughout this country and others.

The COMBINED MODALITY BRANCH implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide specific and immediate clinical trials of combined modality approaches to the therapy of specific tumors. It is responsible for bringing together, under contract, expertise in chemotherapy, surgery, radiotherapy, and immunotherapy in the design of comprehensive therapeutic programs geared to the eventual care of specific disease entities. It is responsible for maintaining continuing liaison with various advisory and consultant groups established as working committees to study the effectiveness of specific types and methods of cancer therapy.

The INVESTIGATIONAL DRUG BRANCH implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide highly specific and immediate clinical trials of anticancer drugs that have demonstrated high activity in animals in the preclinical phase of the drug development aspect of the Cancer Therapy Program. The Branch is responsible for the communication and filing of all information required by the Food and Drug Administration in connection with the Drug Development Program of the National Cancer Institute.

The CLINICAL ONCOLOGY PROGRAM consists of the Medicine Branch, the Pediatric Oncology Branch, the Radiation Oncology Branch, the Surgery Branch, the NCI-VA Medical Oncology Branch, and the Clinical Pharmacology Branch.

The MEDICINE BRANCH is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging and treatment of the malignant lymphomas, breast cancer, ovarian carcinoma, sarcomas, melanoma, cancer of the pancreas, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures related to cancer, such as, bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH including cancer surgery and radiation therapy. The Branch conducts weekly clinical conferences with the departments of Radiation Oncology, Pathology, Clinical Pathology (Hematology), and Radiology on current problems and on the staging of lymphomas. The research program focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is underway in the field of hormone receptors, tumor markers and tissue culture. The Branch conducts weekly laboratory conferences, in conjunction with the Clinical Pharmacology Branch, on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

The PEDIATRIC ONCOLOGY BRANCH practices a combined modality approach to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma, neuroblastoma, aplastic anemia, and histiocytosis. Children and young adults are accepted for treatment. Three areas of clinical investigation are stressed: (a) chemotherapy and immunotherapy; (b) hematologic support and bone marrow transplantation; and (c) diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The Branch is particularly interested in the psychosocial aspects of cancer, and training in this area is emphasized. Candidates with prior training in medicine or in pediatrics may apply to this Branch and may be Board eligible in medical oncology or in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical means followed by chemoimmunotherapeutic manipulations, the goal of which is significant prolongation of remission. Comprehensive immunological assays are performed in order to assess the utility of various techniques in understanding the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. A major area of interest is hematologic reconstitution through autologous bone marrow transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised host. These maneuvers include the use of laminar air-flow isolation and prophylactic antimicrobial agents. Studies on microdetermination of circulating endotoxin and on the molecular identification of latent viral genetic material illustrate newer diagnostic approaches to infectious disease.

In the second year of this program, clinical research training is offered in the three areas previously described. In addition to clinical research, this Branch has a strong program in basic laboratory investigation with emphasis on the molecular biology of tumor viruses, tumor cell biology, molecular and clinical pharmacology, tumor immunology, somatic cell hybridization, and immunohematology. Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates, utilizing excellent collaborative relations with other Branches of the NIH.

The Radiation Oncology Branch has a multidisciplinary orientation with a staff consisting of radiotherapists and medical oncologists. Correspondingly, the clinical emphasis is directed toward combined modality approaches in cancer therapy. Training includes not only experience in chemotherapy but with various diagnostic procedures including bone marrow and liver biopsy, peritoneoscopy, and fiberoptic bronchoscopy. The two-year program includes one year of inpatient care and one year of laboratory investigation. There is continuous outpatient care of selected patients during the entire two years to insure the opportunity for longitudinal observation and management. Finally, while the clinical research programs of the Branch concentrate on specific diseases, experience is gained with a wide spectrum of malignancy by virtue of collaborative studies with other Branches, the above mentioned rotations, and assignment to an oncology consultation service.

The Surgery Branch is a surgical oncology unit emphasizing a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen including melanomas, sarcomas, rectal cancers, and pancreatic cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy as well as the development of new surgical techniques. The laboratory efforts of the Surgery Branch are closely related to its clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The Branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, x-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch staff also serve as general surgeons to the entire National Institutes of Health and see a variety of general surgical consultations not related to the field of cancer.

The NCI-VA Medical Oncology Branch is located outside the Clinical Center at the Veterans Administration Hospital in northwest Washington, D.C. This Branch is concerned with the primary care and clinical investigation of patients with a wide variety of solid tumors and hematologic malignancies. A major effort involves the staging and treatment of small cell carcinoma of the lung. In addition to lung cancer, treatment protocols of stomach, prostatic carcinoma, myeloma, mycosis fungoides, and hepatoma are underway. Associates become experienced in diagnostic procedures, such as bone marrow biopsy, liver biopsy, fiberoptic bronchoscopy, and peritoneoscopy. Programs in the treatment of both acute and chronic leukemias, myelomas, lymphomas, and premalignant hematologic syndromes are being developed with the Division of Hematology. Both veteran and nonveteran patients are admitted for study, and the Branch provides oncology consultation for the hospital.

The Branch laboratory investigations in human tumor cell biology involve studies of oncogenic viruses, molecular biology, cell culture, somatic cell hybridization, and human tumor cell genetics and cytogenetics. *In vitro* models for chemotherapy are under study and clinical investigation of tumor cells kinetics is carried out. The fellowship program is designed to include both clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals. To further this end, close ties and collaboration with the Clinical Center in Bethesda are maintained.

The CLINICAL PHARMACOLOGY BRANCH conducts laboratory and clinical research activities related to problems of drug action and toxicity in man, and as such plays a supporting role for the chemotherapy programs of the other clinical branches of the NCI. Clinical Pharmacology does not have patient care responsibilities of its own, but accomplishes its clinical studies through collaborative ties with the Medicine and Surgery Branches as well as other patient care units. Training opportunities for one or two year assignments are available for post-doctoral fellows, physicians completing one year of clinical training on a clinical unit at the NCI, or for trainees of the Clinical Pharmacology Training Program of the National Institute of General Medical Sciences.

Areas of specific research interest include (1) mechanisms of Adriamycin cytotoxicity; (2) pulmonary metabolism of tissue specific toxins and mutagens; (3) pharmacokinetics and metabolism of established and new antineoplastic agents; (4) clinical and experimental applications of cytofluorometry; and (5) cyclic nucleotide metabolism in human tumor cells.

The DEVELOPMENTAL THERAPEUTICS PROGRAM actively solicits and conducts the search for potential cancer therapeutic agents and subjects them to programmed preclinical evaluation according to a scheme called the Linear Array. In this approach the Developmental Therapeutics Program is responsible for all preclinical phases of development including toxicology and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and a larger extramural program dealing with the major effort in DCT directed towards the preclinical development of therapeutic modalities, in particular those related to chemotherapy.

The LABORATORY OF TOXICOLOGY investigates and describes the qualitative and quantitative toxicity of potential antineoplastic drugs using animal test systems. Attempts are made to define the predictability, reversibility, and mechanism of drug-induced toxicity. A variety of experimental treatment regimens are tested to attain the greatest therapeutic effect at the least cost in serious side effects. The functions of the laboratory are closely integrated with the development of new anticancer agents.

In addition to directing some contracted research, each senior investigator carries on an independent research program. These studies may be broadly defined as biochemical or experimental toxicology and include the following: (1) the biochemical basis of the intoxication brought about by antineoplastic drugs; (2) the detection, quantitation, evaluation, and elucidation of the mechanisms of pathologic alterations produced by various therapeutic modalities in experimental animals and cancer patients; (3) drug interactions; and (4) development and evaluation of predictive experimental animal models for drug toxicity.

The LABORATORY OF MOLECULAR PHARMACOLOGY is engaged in fundamental studies on the mechanisms of drug action on mammalian cells, particularly actions involving nucleic acids and related structures. Of major interest is the question of how chemotherapeutic agents are able to produce selective toxicity against neoplastic cells. These studies center on examination of DNA damage and repair following drug treatment in various types of mammalian cells.

The LABORATORY OF CHEMICAL PHARMACOLOGY evaluates the pharmacological properties of potential and established antitumor agents *in vitro*, in animals and humans. These studies include evaluation of the antitumor activity of single agents as well as adjuvant and combination chemotherapy, studies on the usefulness of other modalities for cancer therapy, mechanism of action studies, structure-activity relationships, dose-response relationships, studies on the mutagenic and carcinogenic potential of antitumor agents, and studies on the disposition of antitumor agents and other model foreign compounds in laboratory animals and humans. The latter studies include the establishment of rates and rate constants which govern the passage of drugs from one body compartment to another. The Laboratory brings together a critical mass of scientists who play an important role in more rational drug design, the use of pharmacological information (plasma levels, tissue levels, metabolism studies) for experimental chemotherapy and earlier development and usefulness of cancer chemotherapeutic agents for the clinic.

The LABORATORY OF TUMOR CELL BIOLOGY is directed towards gaining a better understanding of the processes involved in the molecular control of cellular growth and differentiation, neoplastic transformation, and the pathogenesis of neoplasia with the ultimate goal of developing new and improved approaches for therapy of human malignancies. Intimately related to this program is the search for and development of markers of neoplastic growth which give a quantitative assessment of residual tumor cells after therapy.

The above objectives have been pursued primarily in studies of (1) the purification and properties of enzymes of nucleic acid biosynthesis, particularly the DNA polymerases (DNA-dependent and RNA-dependent) of human normal and leukemic cells and of RNA oncogenic viruses; (2) the biochemical properties of RNA and type-C viruses with special emphasis on determining the mechanism of transcription of RNA to DNA by reverse transcriptases; (3) the origin and oncogenic potential of tumor viruses; (4) leukocyte differentiation *in vitro* using various tissue culture techniques; (5) mechanism(s) of the initiation of DNA synthesis in normal and tumor cells with the development of selective DNA polymerase inhibitors to be evaluated in human normal and leukemic cells; and (6) immunochemical techniques for detecting reverse transcriptase in intact cells and other techniques for detection of viral specific nucleic acids in intact cells.

The LABORATORY OF MEDICAL CHEMISTRY AND BIOLOGY conducts an integrated program for the rational development of antitumor agents. Carries out the synthesis of compounds with potential antitumor activity and assesses the effects of such agents on experimental tumor systems *in vitro* and *in vivo*, and on a variety of potential subcellular target sites; e.g., nucleic acids, cell membranes, microtubular protein, and enzyme systems. Develops analytical methodology for *in vivo* studies with new agents and, where warranted, extends biological studies with such agents to the preclinical and Phase I stages. Manages a contract-supported program to characterize the mode of action of new antitumor agents. The Laboratory stresses rapid and continuous utilization of the data generated from biological studies for the elucidation of structure-activity correlations and for guidance in the synthesis of new antitumor agents of potential clinical value.

The DRUG EVALUATION BRANCH designs, implements, maintains, and coordinates laboratory projects for the recognition, recommendation, and preclinical development of improved therapies against human cancer. This is achieved by (1) screening *de novo*, large numbers of synthetic and natural products for biological activities indicative of clinical utility; (2) detailed evaluation, in appropriate laboratory models, of materials of interest found in primary screens conducted by DEB or in other programs; (3) evaluation of new and established antitumor drugs for conditions of usage which may enhance therapeutic efficacy; e.g., modifications of treatment regimen, combination chemotherapy, combined treatment modalities; and (4) the conduct of fundamental and developmental research aimed at devising improved methods for preclinical drug evaluation. Program design is directed to achieving those goals of the DCT and National Cancer Plan which fall into the scope of Branch functions. Implementation is through the establishment of contracts with qualified research institutions for applied, developmental, and fundamental therapeutic research; for the production and quality control of the experimental laboratory animals used, and for the automated and manual retrieval of laboratory results. DEB staff maintains and coordinates these interrelated contract projects by instructions to contractors regarding program goals in general, and immediate assignments specifically, by insuring scientific and technical sufficiency, and by summarizing laboratory results. End results and recommendations of new therapies for toxicological examination in large animals and for clinical trial are presented to DCT staff via reports to decision groups and to scientific community via formal publication.

The DRUG SYNTHESIS AND CHEMISTRY BRANCH continues to serve as the primary source for receiving new materials from suppliers in the scientific community-at-large and in developing new suppliers. The Branch is responsible for the accessioning process. The Branch with the Drug Synthesis Section (DSS) manages a synthetic chemistry contract program for the development of new drugs and the preparation of analogs for the evaluation by biologists (biochemists, cell biologists, screeners, basic and clinical pharmacologists, etc.). The Chemical and Drug Information Section (CDIS) continues to develop methodology for compound preselection for the screen and the development of a world-wide literature surveillance of data of interest to the Program. The disciplines of the Branch and Sections encompasses all aspects of chemical synthesis, chemical and drug information techniques, including evaluation of chemical, biological screening, toxicological and clinical information relating to analogs and new drug design and syntheses necessary to bring new agents to clinical trial.

In addition, the Branch generates and maintains a record system of all new materials entering the program including their storage and distribution. The processing and custody of all ''Commercial Discreet Agreements'' is also a function of the Branch.

The PHARMACEUTICAL RESOURCES BRANCH is designed to provide comprehensive pharmaceutical services to the DCT. The primary objective of the Branch is to supply high quality chemical substances and formulated products through a coordinated contract-supported program. The major contract support areas include: chemical preparation laboratories, chemical pilot plant production, analytical services, product research and development, and large batch pharmaceutical manufacturing capabilities. Bulk chemicals and formulated clinical products that are commercially available are obtained through NIH direct purchase contract procedures. The initiation of the contracts and the supporting documentation are provided by the Branch staff.

The Branch staff directs contract research in the area of dosage form design and development of unique and effective delivery systems for poorly manageable drugs. A limited in-house formulation research facility is also managed by the Branch to develop dosage forms of high interest to the Program.

The Branch has the additional responsibility for the storage and distribution of all dosage forms used in the various clinical programs.

The NATURAL PRODUCTS BRANCH is engaged in the development of more effective natural product agents for human cancer chemotherapy primarily through contract-supported projects. It will supervise procurement of natural products (world-wide), evaluation of these agents, preparation of large amounts of the active agent, quality control in the preparation of the material and expediting the drug to a stage for toxicological evaluation. Modification of active natural products by chemical and biological transformation to increase therapeutic effectiveness and increase solubility will be done.

Research efforts are directed toward obtaining new natural products through various types of natural product research (continuous fermentation, precursors in cell cultures) and systemically evaluating these new agents plus thoroughly reviewing and testing older compounds in the program vs. new *in vivo* and biochemical screens. The Branch will evaluate new prescreens and initiate biochemical studies on natural products at an earlier time in the program.

The BALTIMORE CANCER RESEARCH CENTER (BCRC) at the University of Maryland Hospital, Baltimore, Maryland, conducts an integrated program of laboratory and clinical research in the therapy and management of cancer patients, including multimodality clinical therapeutic trials, pharmacologic investigations, tumor assay systems, and basic enzymologic and immunologic studies. The program is a collaborative endeavor between the University of Maryland Hospital and the National Cancer Institute, and provides the community with a Referral Oncology Treatment Center. The BCRC is a contributing member of the Acute Cancer and Leukemia Group B, Eastern Cooperative Oncology Group, and the Brain Tumor Study Group.

The CLINICAL ONCOLOGY BRANCH (Chief, Dr. Peter H. Wiernik) conducts a program of clinically-oriented therapeutic research in the support of the Division of Cancer Treatment Program. The Branch operates a 40-bed Inpatient Service and large Outpatient Department, as well as support services contained within one area which provides a close-knit area for continuity of care. Major emphasis is placed on Phase I, II, and III studies, with particular attention to patients harboring adult leukemia and lymphoma, Hodgkin's disease, sarcomas, testicular tumors, and brain tumors. In addition, there are ongoing programs in gastrointestinal cancer, melanoma, breast cancer and lung cancer. Specific research in the preparation and supply of platelets and the collection and transfusion of white blood cells are carried out.

The INFECTION RESEARCH SECTION (Head, Dr. Stephen C. Schimpff) is studying the prevention of infection and support of the infected patient by the use of protected environment areas (Laminar Air-Flow Units) and the use of carefully controlled antibiotic regimens.

The Clinical Research Pharmacy Service, MICROBIOLOGY SECTION (Head, Dr. Viola M. Young) and Data Retrieval and Analysis Unit provide additional support. A rather broad means of pharmacologic and therapeutic evaluations of multi-disciplinary therapy in specific ''signal'' tumors has been developed to evaluate new agents. Patient care is also aided by a computerized Problem-Oriented Medical Information System (PROMIS) with the potential of retrieval and analysis of cancer research treatment data. Combined modality therapy and immunotherapy studies have been initiated. Newer, potentially useful methods of cancer treatment, such as hyperthermia, are also under active investigation. In addition, the BCRC provides consultation to the greater Baltimore medical community, as well as, the University of Maryland Hospital and the VA Hospital in Baltimore. The Clinical Oncology Program is approved by the American Board of Internal Medicine for credit toward certification in Internal Medicine and the subspecialty of Medical Oncology.

The LABORATORY OF CLINICAL BIOCHEMISTRY (Chief, Dr. Nicholas Bachur) is currently engaged in researching problems of clinical importance through the disciplines of cellular biology, biochemistry, physiology, and pharmacology. Emphasis is placed on approaches that can be applied in a coordinated fashion integrating basic and clinical science. The Laboratory studies endogenous factors that regulate cellular growth and differentiation, the mechanisms of cellular blastogenesis, the involvement of cellular membranes in differentiation and cellular recognition, and the chemical control of cellular growth and differentiation. Mammalian materials often are correlated with clinical studies. Expertise is expressed in the areas of cellular biology and ultrastructure, cellular biochemistry, enzymology, biochemical and clinical pharmacology, and in analytical technology.

The LABORATORY OF MOLECULAR BIOLOGY (Chief, Dr. Carl Levy) examines at the molecular level the regulatory pressures to which a cell is subjected during the course of its development. Through the use of sophisticated techniques in the disciplines of both immunology and enzymology, critical evaluation is made of factors within the cell that may cause deviation from normal development. In this respect, emphasis is placed on such factors as enzyme constituents in neoplastic disorders and specific changes of cellular constituents as indicators of the presence of neoplastic disease. The Laboratory investigates the means by which the measurement of human immune responsiveness can be improved and extended. A vital concern of the laboratory is also the development of specific tumor cell marker systems.

The SECTION OF IMMUNOLOGY AND CELL BIOLOGY (Head, Dr. Michael R. Mardiney, Jr.) is involved with studying basic and applied aspects of host immune modulation with particular emphasis on cancer immunology. Programs involving the mechanism of adjuvant activity upon the immune response, as well as the development of techniques for monitoring host immunity to tumor are being carried out.

The SECTION OF NEURO-ONCOLOGY (Head, Dr. Michael D. Walker) is engaged in many aspects of neuropharmacology of brain tumor research. Second year Clinical Associates do basic or clinical research in one of these areas.

NCI INFORMATIONAL BULLETIN

Prospective applicants to the National Cancer Institute may obtain an NCI Informational Bulletin by writing Dr. Alan Rabson, Director, DCBD, NCI, Building 31, Room 3A03, National Institutes of Health, Bethesda, Md. 20014.

National Eye Institute

Carl Kupfer, M.D., Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three Clinical Associates from those candidates who have completed an accredited 3-year ophthalmology program. Clinical Associates spend time in both clinical and laboratory research, including patient care activities.

In selection of Clinical and Research Associates, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

Laboratory and Clinical Research

The National Eye Institute has developed its clinical and research program into two major branches, the Laboratory of Vision Research and the Clinical Branch. The Laboratory of Vision Research plans and conducts fundamental laboratory research on the visual system. This includes anatomy, biochemistry, physiology, embryology, pharmacology, and experimental pathology of the visual system.

The CLINICAL BRANCH plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of disorders of the visual system. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the Clinical Branch's responsibility to investigate the causes and prevention of blindness. The major areas under study are cataracts of unusual origin, including congenital cataracts, glaucoma, neuro-ophthalmology, ophthalmic genetics, vascular diseases, retinal degenerations, and ophthalmic pathology.

(1) Cataracts of unusual origin and congenital cataracts are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

(2) Neuro-ophthalmology: Patients from the ophthalmic and neurologic services are being studied using advanced methods for electro-oculography, pupillometry, video tape recording, and computer analysis. The main emphasis of these studies at present is on cerebellar disorders that affect ocular movements.

(3) Glaucoma: Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is underway.

Innovative surgical techniques are being assessed in selected cases of hemorrhage and congenital glaucoma and in cases in which anti-glaucoma surgery has failed.

Axoplasmic flow is being studied in optic nerves of glaucomatous monkeys, and the properties of trabecular meshwork are being studied in tissue culture.

(4) Ophthalmic genetic studies include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogeneses of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism and abnormalities of the anterior chamber angle associated with glaucoma.

(5) In vascular diseases, investigations are being conducted to define underlying mechanisms in conditions such as diabetic retinopathy, macular degenerations, and other retinal vascular diseases or vascular disease of the optic nerve. A controlled clinical trial of anti-coagulation and thrombolytic agents in occlusion of the central retinal vein is underway.

(6) Ophthalmic Pathology: Eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied histopathologically and electron microscopically. Many of these eyes are from subjects who have rare or unusual metabolic diseases or who have been subjected to prolonged courses of anti-cancer treatment. There is opportunity for close collaboration with investigators in the Laboratory for Vision Research in the Eye Institute.

The LABORATORY OF VISION RESEARCH is composed of the following disciplines:

BIOCHEMISTRY. This section is conducting studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolisms of photoreceptors are also under investigation. Finally, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

EXPERIMENTAL EMBRYOLOGY. The goals of this section are to identify and characterize the myriad tissue interactions which control the orderly growth of the vertebrate eye and assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the species and tissue specificities of these interactions, and the nature of these tissue interactions which control morphogenesis.

Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. In particular, attention is being focused on newly discovered, cell-free, collagen containing ''initiator layers'' which are transiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

EXPERIMENTAL PATHOLOGY. Research being conducted in this section of the laboratory centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

NEUROPHYSIOLOGY. Investigations in this section are currently underway to better understand the cellular organization underlying visual perception. Studies are being conducted on the responses of single nerve cells at various levels in the visual nervous system of mammals. The purpose of this work is to understand how nerve cells contribute to visual sensations such as color, shape, movement, depth, etc. The technique employs fine microelectrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an experimenter to stimulate the retina with spots or slits of colored lights whose movement and shape can be quantitatively controlled. It involves electrophoresing dye into single cells whose responses have been studied and then finding these cells within the brain or retina.

By this means both the structure and function of nerve cells can be correlated and the underlying circuitry of the visual system understood. The approach requires close interaction between single cell physiology and cellular anatomy at the light and electron-microscopic level.

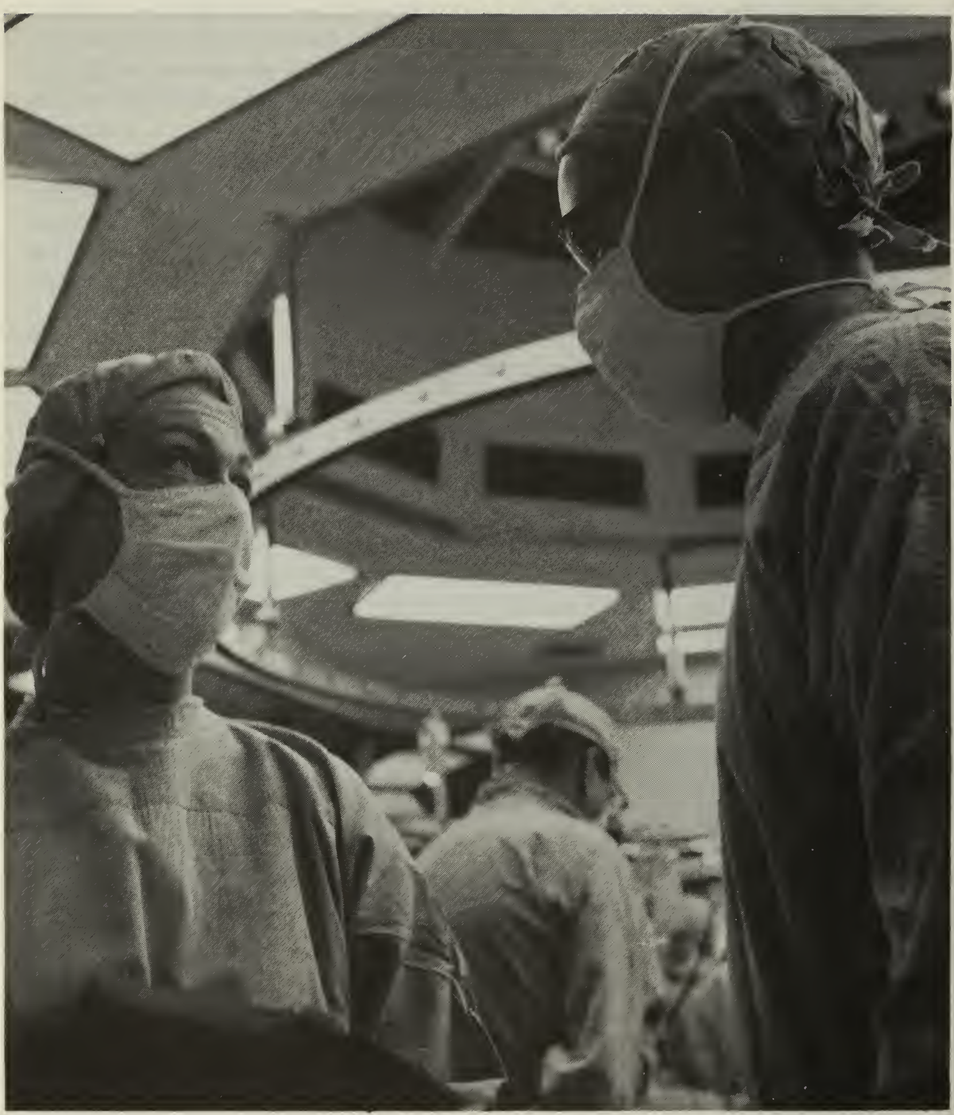
RETINAL AND CORNEAL METABOLISM. Members of this section are investigating the function of the retina, pigment epithelium, and cornea in relation to clinical diseases such as retinitis pigmentosa and keratomalacia.

The mechanism by which visual cells detect light and produce neural messages is not known. Calcium may play a role in the process since it mimics the effects of light on the retina and is found in very high concentrations in pigment epithelium and retinal photoreceptors. Small intracellular messengers called cyclic nucleotides have also been found in extraordinarily high concentrations in retinal photoreceptors. Since light markedly affects their concentration, they, too, are probably intimately involved in the visual process. A method of injecting various substances into visual cells is now being developed to determine directly the effect of these substances on the visual process in both normal and pathologic conditions.

Studies on the synthesis and degradation of the visual protein rhodopsin have helped explain how retinal photoreceptors are renewed. Defects in this process may underlie some forms of retinal degeneration; thus, studies using dystrophic retinas of test animals are underway to compare the process of photoreceptor renewal in normal and pathologic conditions. Substances such as hormones and neurotransmitters which affect the normal growth and development of retinal cells in tissue culture are being assessed. Several of these have already been identified and are being further studied in relation to their role in retinal function.

Specific receptor molecules for vitamin A have been found in retina and pigment epithelium. These receptors are probably involved in the normal uptake, distribution and retention of the vitamin in the visual system. Differences in receptor concentrations in retinas of normal humans and patients with retinitis pigmentosa have been found.

Vitamin A receptors are also present in the cornea and conjuctiva. The possible relationship of these receptors to corneal disease is being considered. Other aspects of corneal physiology, such as glutathione metabolism, are under investigation. Such studies are important not only for understanding corneal function and transparency but for improving corneal transplant and surgery techniques as well.



National Heart, Lung, and Blood Institute

Jack Orloff, M.D., Director of Intramural Research
Harry R. Keiser, M.D., Clinical Director

Associate Program in Medicine, Surgery, and the Basic Sciences

The National Heart, Lung, and Blood Institute currently appoints three Research Associates and six Clinical Associates in medicine for a 2-year period beginning each July 1. Several Staff Associates are also appointed in one or more of the Institute's laboratories. For those who are interested in lengthening their period of research experience, these appointments may usually be extended, by mutual agreement, for a third year. Four to five Clinical Associates are also appointed for 2-year periods in surgery.

Research and Clinical Associates in Medicine

Candidates for Research and Clinical Associate positions have only one interview in this Institute. Associates are interviewed by a committee made up of the Director of Intramural Research, the Clinical Director, and a Chief of one of the Institute's laboratories or branches. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the NHLBI. After appointment and prior to entering on duty, each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the Associate and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. (On the basis of past experience, it appears virtually certain that each Associate will be able to work with the group of his choice.) The level of research responsibility and freedom will depend upon his training and experience as well as his desires.

Each Associate in medicine will devote his time primarily to research in the laboratory under the immediate supervision of a preceptor in an area of his selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of his laboratory.

RESEARCH ASSOCIATES. These appointments are designed to give physicians an opportunity to improve their background for a career in basic medical research. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. No clinical assignments are involved (unless the Associate has chosen a laboratory involved directly in clinical investigation), but the Associates are welcome to attend any of the clinical teaching exercises.

CLINICAL ASSOCIATES. These appointments are designed to give physicians training in both clinical and basic research. Candidates must have completed a minimum of two years of training in a residency program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the Clinical Associateship will be credited as a third year of training in internal medicine by the American Board of Internal Medicine.

Clinical Associates will be responsible, under the guidance of investigators on the Heart, Lung, and Blood Institute staff, for the medical care of patients during 10 of the first 12 months of their service. During this time they will rotate through the four medical services that serve the clinically oriented branches of the Institute. These services occupy 75 beds and include: (1) Cardiology, (2) Hypertension-Endocrinology, (3) Lung, and (4) Hematology and Metabolism.

The clinical period is one of intensive training under direction of the Clinical Director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The Clinical Associate devotes both his time off the wards and a full 14 months of his 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the optional third year for Associates who have chosen nonclinical laboratories.

STAFF ASSOCIATES. Laboratories within the Heart, Lung, and Blood Institute sometimes have openings for Staff Associates appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Check List for the Institute. Selections for those positions are made by the Chief of the Laboratory. The position of Staff Associate is otherwise comparable to that of Research Associate.

CLINICAL ASSOCIATES IN SURGERY. The Surgery Branch of the National Heart, Lung, and Blood Institute appoints four to five Associates in Surgery for a 2-year period beginning each July 1. The program is primarily designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in a research or academic atmosphere. Candidates must have completed an internship and at least 1 year of surgical residency by the starting date of their appointment.

STAFF ASSOCIATES IN EPIDEMIOLOGY. The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood, and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental, and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or one of the field programs. The Associateships may begin after internship or after 1 year of training in a clinical residency or school of public health. Candidates interested in this possibility are encouraged to write to Dr. Manning Feinleib, Chief, Epidemiology Branch, National Heart, Lung, and Blood Institute, Bethesda, Md. 20014, for more detailed information about specific assignments.

JOINT ENDOCRINOLOGY TRAINING PROGRAM. Clinical Associates from the National Heart, Lung, and Blood Institute may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to qualify Associates for the Endocrinology Subspecialty Boards. National Heart, Lung, and Blood Institute participants will spend 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the Associate will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the Associate's 3 years will be spent primarily in research activity within the National Heart, Lung, and Blood Institute, although he will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two Associates to enter this program in any one year.

Formal Instructions

The major form of didactic postgraduate instruction is through the evening courses offered by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Research, Clinical, and Staff Associates are expected to take advantage of this academic work.

Laboratories, Branches, and Sections

The laboratories, branches, and sections of the National Heart, Lung, and Blood Institute, all of which are open to Clinical and Research Associates for their research work, are listed below with the names of their chiefs and a brief summary statement indicating the breadth of activities. Candidates desiring further information may obtain a current bibliography summarizing the activities of the current staff by writing to Dr. Jack Orloff, Director of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, Md. 20014.

Section on Theoretical Biophysics (Chief, Dr. John L. Stephenson). The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned both with the formulation of theoretical models and with the development of mathematical and computational methods for their analysis. Currently much of the research in the section centers on the mechanism of urine formation in the mammalian kidney.

Laboratory of Biochemical Genetics (Chief, Dr. Marshall Nirenberg).

Section on Molecular Biology (Chief, Dr. Marshall Nirenberg). This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, i.e., genetic programs for differentiation that determine informational reactions of neurons. Systems and problems involve the culture of mammalian cells and hybrid cells, and gene function for informational molecules such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

Section on Macromolecules (Chief, Dr. Alan Peterkofsky). Studies of regulatory mechanisms involved in nucleic acid and protein biochemistry. Current emphasis is on regulation of cyclic AMP metabolism in microbial systems as well as mammalian protein synthesis.

Laboratory of Biochemistry (Chief, Dr. Earl R. Stadtman).

Section on Enzymes (Chief, Dr. Earl R. Stadtman). Studies of diverse enzyme systems that offer unique opportunities to elucidate a number of basic biochemical phenomena, namely, those concerned with vitamin-coenzyme function, the cellular regulation of metabolism, the energy-dependent transport of metabolites across membrane barriers, and mechanisms of enzyme action.

Section in Intermediary Metabolism and Bioenergetics (Chief, Dr. Thressa C. Stadtman). This section is concerned primarily with investigations on the mechanisms of anaerobic amino acid dissimilation and phosphorylation coupled with anaerobic electron transfer processes. Special emphasis is on the roles of various coenzymes (*viz*, vitamin B_{12} coenzyme, CoA, pyridoxal phosphate, flavins, pyridine nucleotides, lipoic acid, and naphthoquinones) and of various electron transfer proteins (*viz*, selenoproteins, ferridoxins, flavoproteins and sulfhydryl proteins) in these processes.

SECTION ON PROTEIN CHEMISTRY (Chief, Dr. Ann Ginsburg). Studies on protein structure are directed toward understanding protein-ligand interactions, protein-protein interactions, and enzyme catalysis and regulation.

LABORATORY OF CELL BIOLOGY (Chief, Dr. Edward D. Korn). This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

SECTION ON CELLULAR BIOCHEMISTRY AND ULTRASTRUCTURE (Chief, Dr. Edward D. Korn). This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the biochemistry of the plasma membrane in relation to endocytosis and the molecular and ultrastructural basis of cell motility. Cytoplasmic actin, myosin, and related proteins are purified and their interactions studied and compared to their muscle counterparts. Opportunities are available for research and training in biochemistry and electron microscopy.

SECTION ON CELLULAR PHYSIOLOGY (Chief, Dr. Evan Eisenberg). This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin and the troponins. Emphasis is on kinetic studies with pure proteins.

SECTION ON MEMBRANE ENZYMOLOGY (Chief, Dr. Richard Hendler). This section studies enzyme systems that require organization on or interaction with membranes in order to insure their proper functioning. The synthesis of DNA by enzyme complexes and the electron transport chain of *E. coli* are presently being investigated.

SECTION ON ORGANELLE BIOCHEMISTRY (Chief, Dr. Martin Flavin). This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the physiological regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

LABORATORY OF CELLULAR METABOLISM (Chief, Dr. Martha Vaughan). Major areas of research interest are: (1) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides in regulation of growth and metabolism of mammalian cells grown in culture; and (2) elucidation of the means through which certain hormones and humoral agents (e.g., insulin, prostaglandins, adrenal steroids, kinins, biogenic amines) affect the formation, degradation and/or action of cyclic nucleotides in several types of mammalian cells.

LABORATORY OF CHEMICAL PHARMACOLOGY (Chief, Dr. James R. Gillette).

SECTION ON DRUG-ENZYME INTERACTION (Chief, Dr. James R. Gillette). This section studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objective has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

SECTION ON PHYSIOLOGY (Chief, Dr. Harriet M. Maling). This section studies interactions of drugs, particularly the mechanisms by which various treatments may alter the hepatotoxicity or pulmonary toxicity induced by various organic compounds. This includes study of how hepatotoxicity may be correlated with the covalent binding of metabolites to liver lipids and proteins, the formation of lipid peroxides, and effects on microsomal enzymes. This also includes studies of modifications of toxicity produced by treatments which alter substantially the body clearance of a compound.

SECTION ON DRUG-TISSUE INTERACTION (Chief, Dr. Gopal Krishna). This section is involved in the study of the initial events occurring in cells as the result of a variety of drug (hormone)-cell interactions. This section has been studying the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, it has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

LABORATORY OF CHEMISTRY (Chief, Dr. Henry M. Fales). Conducts research into methods for the structural analysis of organic compounds specifically via mass spectrometry, X-ray crystallography, nuclear magnetic resonance, etc., in addition to classical methods of chemical degradation. Also studies biosynthetic pathways via tracer techniques and chemical synthesis.

SECTION ON PHYSIOLOGICAL CHEMISTRY (Chief, Dr. John I. Pisano). Normal and pathologic states in man are studied at the molecular level by advanced analytical techniques. Under investigation are the prostaglandins and vasoactive peptides (e.g., bradykinin and angiotensin), precursor proteins of the peptides and the enzymes involved in their biosynthesis and degradation. Research is currently directed to the study of hypertension, coagulation, and fibrinolysis.

LABORATORY OF EXPERIMENTAL ATHEROSCLEROSIS (Chief, Dr. Donald L. Fry). The laboratory program is directed toward experimental evaluation of the pathological, physiological, biophysical, chemical, and histological processes involved in the genesis of atherosclerosis. These studies are carried out with tissues from both animal colonies and human subjects.

SECTION ON VASCULAR PHYSIOLOGY (Chief, Dr. Donald L. Fry). Studies the relationship of physical-chemical and hemodynamic forces to the processes of transvascular transport of atherogenic precursor molecules into the vascular tissue space and the response of the cellular and structural elements of the wall to these forces and substances.

SECTION ON COMPARATIVE ATHEROSCLEROSIS AND ARTERIAL METABOLISM (Chief, Dr. Robert W. Mahley). Studies the origin and fate of plasma lipoproteins in experimental animals and man in relation to arterial wall metabolism and atherosclerosis. Primary emphasis is on lipid and protein chemistry, response of arterial cells grown in tissue culture, and comparative atherosclerosis.

LABORATORY OF KIDNEY AND ELECTROLYTE METABOLISM (Chief, Dr. Maurice B. Burg).

SECTION ON ELECTROLYTE TRANSPORT (Chief, Dr. Jack Orloff).

SECTION ON RENAL MECHANISMS (Chief, Dr. Maurice B. Burg).

SECTION ON MEMBRANE METABOLISM (Chief, Dr. Joseph S. Handler). This section conducts research on the mechanism and regulation (hormonal and otherwise) of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, toad bladder, and erythrocytes. Electrophysiology and intermediary metabolism as related to transport are emphasized.

LABORATORY OF MOLECULAR HEMATOLOGY (Chief, Dr. W. French Anderson). This laboratory is concerned with investigations into the mechanism and regulation of mammalian gene expression and protein synthesis. Areas of research include cell-free hemoglobin synthesis directed by isolated mRNA, purification and characterization of mammalian initiation and elongation factors, enzymatic synthesis of hemoglobin genes using globin mRNAs as templates, and studies on globin gene expression using mouse erythroleukemia cells and somatic cell hybrids. Joint studies are also carried out with the Clinical Hematology Branch.

LABORATORY OF TECHNICAL DEVELOPMENT (Chief, Dr. Robert L. Bowman). Conducts research into instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicromethods to practical clinical instrumentation.

SECTION ON BIOPHYSICAL INSTUMENTATION (Chief, Dr. Robert L. Berger). This section develops methods and instruments based on new technology of physical and computer science applicable to measurements of reaction kinetics, molecular structure and chemistry of substances of biomedical interest. Current work is directed at developing methods involving calorimetry, Mossbauer spectroscopy, laser photolysis, fast spectroscopic and fluorometric systems.

SECTION ON PULMONARY AND CARDIAC ASSIST DEVICES (Chief, Dr. Theodor Kolobow). Conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This program includes the development of improved blood oxygenators, blood pumps, and control systems.

CARDIOLOGY BRANCH (Chief, Dr. Stephen E. Epstein)

SECTION ON CARDIOVASCULAR DIAGNOSIS (Acting Chief, Dr. Kenneth Kent). Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by heart failure.

SECTION ON EXPERIMENTAL PHYSIOLOGY AND PHARMACOLOGY (Chief, Dr. Stephen E. Epstein). Research objectives are aimed towards an understanding of the physiologic, anatomic, and biochemical mechanisms responsible for control of the normal heart and circulation, an elucidation of the alterations produced by ischemic and nonischemic heart disease, and an evaluation of interventions designed to reverse the biochemical and, thereby, the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic and echocardiographic (one- and two-dimensional systems) studies in man, electron microscopic and biochemical studies of tissues obtained from human surgical specimens as well as from the experimental animal, and pharmacological investigations in man and animals.

SECTION ON MOLECULAR CARDIOLOGY (Chief, Dr. Robert S. Adelstein). Current investigations are directed toward an understanding of the function and control of the contractile proteins of muscle and non-muscle cells. The role of myosin phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include: (1) Myosin phosphorylation in smooth, cardiac and skeletal muscle; (2) myosin phosphorylation and control of kinases and phosphatases in platelets, pre- and post-fusion myoblasts and HeLa cells; and (3) contractile proteins and their role in cell proliferation.

CLINICAL HEMATOLOGY BRANCH (Chief, Dr. Arthur W. Nienhuis). This branch applies the techniques of cell and molecular biology aimed toward understanding and treating human disorders of hemoglobin synthesis and erythroid differentiation. Major research areas include the cellular and molecular mechanisms of regulation of the individual globin genes during erythroid differentiation. Patients with a broad range of red blood cell diseases are studied on the clinical service. Intracellular factors which influence the binding of oxygen to hemoglobin are being explored, particularly as they pertain to the deoxygenation and intracellular gelation of sickle hemoglobin. The value of iron chelation therapy in patients with transfusional hemosiderosis is under investigation. Joint studies are also carried out with the Laboratory of Molecular Hematology.

HYPERTENSION-ENDOCRINE BRANCH (Chief, Dr. Frederic C. Bartter). This branch represents a merger of the previous Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension, but its activities are wide-ranging, as indicated by the description of section activities.

SECTION ON STEROID AND MINERAL METABOLISM (Chief, Dr. Frederic C. Bartter). The principal research of this section is directed towards the pathophysiology of hypertension. It is broadly approached through clinical, physiological, and biochemical studies on steroid metabolism; on the renin-angiotensin system; on the kallikrein-kinin system; on the sympathetic nervous system, including catecholamines; on prostaglandins; and on the interrelations of each of the above with mineral metabolism and the kidney. Other research of this section involves the functions of the adrenal glands, and the pituitary gland, and their interrelationships with the kidneys, and studies on a wide variety of other endocrine disorders. There is strong emphasis on chronobiology and chronopharmacology.

SECTION ON EXPERIMENTAL THERAPEUTICS (Chief, Dr. Harry R. Keiser). A wide spectrum of research opportunities is offered, ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins and cathecholamines, conducted both in man and in experimental animals. Other current studies encompass disorders of serotonin and histamine.

SECTION ON BIOCHEMICAL PHARMACOLOGY (Chief, Dr. Walter M. Lovenberg). This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of the enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is a prime objective, and investigations are extended from the molecular level to experimental animals and man.

MOLECULAR DISEASE BRANCH (Chief, Dr. H. Bryan Brewer). The activities of this branch are concerned primarily with the metabolism and transport of lipids. This includes the structure and relationships of lipoproteins and their apoprotein constituents, and the nature of enzymes involved in fat metabolism and the regulation of their activities, particularly as they control the concentrations of lipids in plasma and tissues. A major interest is familial lipoproteinemia and other metabolic diseases, especially those which are genetically determined, and related to lipid transport, metabolism and to atherosclerosis. The activities of the sections are integrated in such a way that, if they wish, Associates may participate in collaborative work involving several sections.

SECTION ON PEPTIDE CHEMISTRY (Chief, Dr. H. Bryan Brewer). Research is directed toward the analysis and structure of polypeptide hormones and lipoproteins with the object of developing knowledge of structure-function relationships.

SECTION ON LIPOPROTEIN STRUCTURE AND FUNCTIONS (Chief, Dr. Peter Herbert). Research is concerned with isolation, identification, and structure of apolipoproteins, and elucidation of their special functions and interrelationships.

MOLECULAR HEMATOLOGY BRANCH (Chief, Dr. W. French Anderson). This branch is concerned with investigations into the mechanism and regulation of mammalian gene expression and protein synthesis, specifically relating to hemoglobin and to diseases involving the regulation of hemoglobin synthesis.

SECTION ON MOLECULAR GENETICS (Chief, Dr. W. French Anderson). This section conducts investigations into the mechanism and regulation of hemoglobin biosynthesis. Studies include cell-free hemoglobin synthesis directed by isolated mRNA, purification and characterization of mammalian initiation and elongation factors, globin mRNA transcription from bone-marrow chromatin, and attempts to synthesize a DNA gene coding for globin mRNA with the use of the enzyme reverse transcriptase.

PATHOLOGY BRANCH (Chief, Dr. William C. Roberts). This Branch is concerned with the study of morphologic aspects of cardiovascular disease and their correlation with functional derangements. Morphologic analyses include electron microscopy.

PULMONARY BRANCH (Chief, Dr. Ronald G. Crystal). Research in this branch is designed to approach the structure and function of the lung through cellular and biochemical methods. Both laboratory and clinical investigations are conducted.

SECTION ON PULMONARY BIOCHEMISTRY (Chief, Dr. Ronald Crystal). Investigation of the biochemical basis of lung function in health and disease using techniques of protein chemistry, molecular biology, tissue culture, and immunology, with specific emphasis on the regulation of synthesis and degradation of connective tissue elements. Clinical research is directed toward correlating physiologic, biochemical, and morphologic observations in patients with interstitial lung disease, destructive lung disease, hereditary disorders of connective tissue, and hypersensitivity lung disease.

SURGERY BRANCH (Chief, Dr. Andrew G. Morrow).

National Institute of Allergy and Infectious Diseases

Franklin A. Neva, M.D., Acting Scientific Director
Michael M. Frank, M.D., Clinical Director
Anthony S. Fauci, M.D., Deputy Clinical Director

The NIAID annually appoints Associates for the laboratories described below. Clinical Associates are selected by the Clinical Director, appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Research Associate appointments in the other laboratories may begin after internship or residency training. In general, those appointments which begin after 1 or more years of residency training have some degree of responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Appointees through the Early Commissioning Program will be regarded as are appointees through other programs. Final identification as to positions for which they are being considered and as to whether the position will afford 1 or more years of residency training before entry will be made to prospective candidates at the time of interview.

Specific answers to any questions or additional information may be obtained by applicants from Scientific Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. 20014. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be specific as possible as to interests of applicant and information desired.

The LABORATORY OF CLINICAL INVESTIGATION (Michael M. Frank, M.D., Chief).

The National Institute of Allergy and Infectious Diseases appoints six to eight Clinical Associates. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned primary clinical responsibilities are made during the second or third year except as dictated by the needs of the Clinical Associates' research.

There are 52 research beds. Clinical Associates consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each Clinical Associate selects his own area of investigative interest under the general preceptorship of the Clinical Director and the senior members of the staff of the Laboratory of Clinical Investigation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the Clinical Associate works, the subspecialty boards in infectious diseases or allergy will usually credit the training received towards admission to these board examinations.

Opportunities exist for research in a wide variety of areas of infectious and immunological disease. Examples of studies now in progress are:

- The etiology and pathogenesis of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- Pathogenesis of both experimental and clinical fevers.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Mechanisms of regulation of immune reactivity in normals and in patients with immunologically mediated diseases.

- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma and allergic diseases.
- The role of immune complexes in the production of disease.
- The application of electron microscopy, autoradiographic, and cytochemical techniques to studies of cellular interactions in immunologic information processing both in humoral and cellular events.
- The interrelationship of coagulation and fibrinolysis to kinin generation and the role of these enzymatic pathways in the pathogenesis of reactions of the immediate hypersensitivity type.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Study of chronic bacterial pulmonary infections.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Dr. Franklin A. Neva, Acting Scientific Director.

Research Areas and Senior Staff
Allergic Diseases—Allen P. Kaplan, M.D., Michael A. Kaliner, M.D.
Biologic Structure—Alan S. Rosenthal, M.D.
Clinical Allergy and Hypersensitivity—Charles H. Kirkpatrick, M.D.
Clinical Immunology—Michael M. Frank, M.D.
Clinical Mycology—John E. Bennett, M.D., Kyung J. Kwon-Chung, Ph.D.
Clinical Parasitology—Franklin A. Neva, M.D., Eric A. Ottesen, M.D.
Clinical Physiology—Anthony S. Fauci, M.D., John I. Gallin, M.D., Charles A. Dinarello, M.D.
Medical Virology—Raphael Dolin, M.D.

The LABORATORY OF VIRAL DISEASES (Wallace P. Rowe, M.D., Chief) conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses, and on host antiviral defense mechanisms.

Studies of tumor viruses are concentrated on murine leukemia viruses, adenovirus-SV40 hybrid viruses, and human papovaviruses. These studies include investigations of the interactions between defective and competent viruses, the natural history and epidemiology of tumor viruses, genetic transmission of leukemia viruses in mice, and the viral and host genetic factors of importance in viral tumorigenesis.

The mechanism of action of interferon and inducers of interferon is studied by biological and biochemical approaches; the development and evaluation of new interferon inducers for possible clinical application are also undertaken.

Other areas of study are the biology of parvoviruses and the recently discovered viruses of certain medically important protozoa.

Research Areas and Senior Staff
Leukemia Viruses—Wallace P. Rowe, M.D., Janet W. Hartley, Ph.D.
Adeno-SV40 Hybrid Viruses—Andrew M. Lewis, Jr., M.D.
Papovaviruses—Kenneth K. Takemoto, Ph.D.
Parvoviruses—Malcolm D. Hoggan, Sc.D.
Interferon—Hilton B. Levy, Ph.D.
Amebal Viruses—Carl F. T. Mattern, M.D., M. Katherine Cook Jaouni, Ph.D.

The LABORATORY OF BIOLOGY OF VIRUSES (Norman P. Salzman, Ph.D., Chief) is primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain specific antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for Associates is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff
- Biochemical Virology—Norman P. Salzman, Ph.D.
- Macromolecular Biology—Bernard Moss, M.D., Ph.D.
- Molecular Structure—James A. Rose, M.D.
- Physical Biochemistry—Malcolm A. Martin, M.D.

The LABORATORY OF INFECTIOUS DISEASES (Robert M. Chanock, M.D., Chief) is concerned with the basic behavior of viral and mycoplasmal pathogens which play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as coronaviruses and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycoplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff
- Epidemiology—Albert Z. Kapikian, M.D.
- Hepatitis Virus—Robert H. Purcell, M.D.
- Mycoplasma—Joseph G. Tully, Ph.D.
- Respiratory Viruses—Robert M. Chanock, M.D.

The LABORATORY OF IMMUNOLOGY (William E. Paul, M.D., Chief) is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in both the prevention and pathogenesis of human diseases.

Areas of active investigation now include the study of the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells.

Further, active studies of the role of different lymphocyte classes in a variety of human diseases are underway, and models for the study of the role of cellular immune responses in tumor immunity and for the investigation of immunotherapy of tumors are being developed.

Associates will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff
  Cellular Immunology and Genetic Regulation of the Immune Response—Ira Green, M.D., Donald E. Mosier, M.D., Ph.D., William E. Paul, M.D., Ronald H. Schwartz, M.D., Ph.D., Ethan M. Shevach, M.D.
  Immunochemistry and Immunogenetics—John K. Inman, Ph.D., Rose Lieberman, Rose G. Mage, Ph.D., Myron J. Waxdal, Ph.D.

The LABORATORY OF MICROBIAL IMMUNITY (Richard Asofsky, M.D., Chief) is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunological methods, offer the Associate comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution, and susceptibility of the interacting components to various treatments which suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations. Autoimmune phenomena are studied using immune complex nephritis as a model. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The relationship of this disease to the presence and activity of such integrated viruses as the murine leukemia agents are studied. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff
  Biochemistry—Benjamin Prescott, Ph.D.
  Experimental Pathology—Richard Asofsky, M.D.
  Microbiology and Immunology—Philip J. Baker, Ph.D.

The LABORATORY OF PARASITIC DISEASES (Franklin A. Neva, M.D., Chief) is engaged in both basic and applied studies of parasitic diseases of man. Basic research is conducted with a variety of parasities such as leishmania, trypansomes, malaria, amebae, toxoplasma, schistosomes, filaria, and tapeworms. Current studies include comparative mechanisms of energy transfer, non-heme iron respiratory proteins, ultrastructure of parasites, and *in vitro* host-parasite interactions at the cellular level utilizing specialized optical techniques. Increasing emphasis is being devoted to consideration of immunologic response of the host in parasitic infections, both humoral and cellular, and to biochemical and immunological characterization of parasite surfaces. Some experimental infections of animals, such as malaria, leishmaniasis, and filariasis are utilized as models of naturally occurring disease in man. Availability of different species of simian parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate circumstances permit, certain problems are studied in the field in collaboration with local institutions. A Section of Clinical Parasitology is maintained within the Laboratory of Clinical Investigation providing a mutually useful opportunity for clinical studies.

The Pacific Research Section in Hawaii (under the direction of Dr. Leon Rosen) conducts research on vector-borne viral diseases as well as certain parasitic and other diseases of particular importance to the Pacific area. The isolated ecologic environment of the Pacific Islands is utilized for epidemiologic investigations. Current work is mainly on dengue hemorrhagic fever, swine influenza, and venereal diseases.

Within reasonable limits and with guidance of senior staff, associates can select their area of work and a preceptor. In addition, an organized program provides associates a broad exposure to medical parasitology including clinical aspects.

Research Areas and Senior Staff

Cell Biology and Immunology—Harley G. Sheffield, Ph.D.
Host-Parasite Relations—Allen W. Cheever, M.D.
Malaria—Louis H. Miller, M.D.
Parasitic and Vector-borne Viral Diseases, Pacific Area—Leon Rosen, M.D.
Parasite Growth and Differentiation—Louis S. Diamond, Ph.D.
Physiology and Biochemistry Section—Eugene C. Weinbach, Ph.D.

The LABORATORY OF STREPTOCOCCAL DISEASES (Roger M. Cole, Ph.D., M.D., Chief) investigates the genetics of streptococci and their bacteriophages, particularly in relation to ultrastructure, cell wall and surface composition, antigenic structure, competence, and autolytic enzymes. Current studies utilize phage-mediated transduction in group A streptococci; and transduction, DNA-mediated transformation and transfection, and lysogenization in group H streptococci. Efforts are directed to genetic transfer of natural characteristics (i.e., other than antibiotic resistance) which may alter epidemiological patterns in human disease. Emphasis is on surface antigens which can, if changed, result in differences in virulence, immunogenicity, phage susceptibility, adherence, and serologic recognition.

Other studies include virus-host reactions of newly-discovered viruses (phages) of some mycoplasmas; host-parasite interactions of gonococci; and the nature and role of cell wall and membrane components of staphylococci.

Associates have opportunities for training and experience in electron microscopy, microbial genetics, phage virology, and appropriate bacteriologic and biochemical methods related to the above or similar areas of investigation.

Research Areas and Senior Staff

Streptococci and Bacteriophages—Roger M. Cole, Ph.D., M.D.

Microbial Genetics—Jon M. Ranhand, Ph.D.
Microbial Composition and Function—Eskin Huff, Ph.D.; Theodore S. Theodore, Ph.D.
Microbial Ultrastructure—Roger M. Cole, Ph.D., M.D.

The ROCKY MOUNTAIN LABORATORY (Herbert G. Stoenner, D.V.M., Director) located at Hamilton, Mont., is internationally recognized for research on rickettsial and tick-borne diseases. The laboratory is a WHO Reference Center for Human Rickettsioses. In medical entomology and acarology, principal projects include biology and systematics of ticks and mites, ecology of selected tick- and mosquito-borne viruses, and general and subcellular relationships between arthropod-borne microbiota and their vectors as studied by various approaches, including arthropod tissue culture and electron microscopy.

Various aspects, particularly immunology and microbiology, of selected infectious diseases are under investigation. Scrapie, progressive pneumonia of sheep, Aleutian disease and encephalophathy of mink are studied as models of chronic degenerative diseases of man. Studies are made on pertussis, rabies, tularemia, murine leukemias, pathogenic fungi, and the PTL group of organisms. More basic inquiries are made into fundamental mechanisms in delayed hypersensitivity, cell-mediated immunity, and antibody production according to immunoglobulin class.

The fractionation of microbial agents, such as *Mycobacteria*, *Bordetella*, and gram-negative organisms, by special biophysical and biochemical methods and the role of these subcellular fractions in immunity, hypersensitivity, tumor immunology, and other host responses are subjects of major investigations.

Opportunities for training associated with these research projects are provided in comparative pathology, electron microscopy, scanning electron microscopy, virology, immunology, immunochemistry, and a wide variety of specialized biophysical and biochemical methodology.

Research Areas and Senior Staff
Allergy and Immunology—John J. Munoz, Ph.D., Robert K. Bergman, Ph.D., Bruce W. Chesebro, M.D., John E. Coe, M.D., Herbert F. Hasenclever, Ph.D., Donald L. Lodmell, Ph.D., John L. Portis, M.D.
Slow Viral Diseases—William J. Hadlow, D.V.M., Richard E. Race, D.V.M.
Epidemiology—Robert N. Philip, M.D., Elizabeth A. Casper, M.S.P.H., Leo A. Thomas, Ph.D.
Medical Zoology and Zoonotic Diseases—J. Frederick Bell, M.D., Carleton M. Clifford, Jr., Ph.D., James E. Keirans, Ph.D., Conrad E. Yunker, Ph.D.
Molecular Biology—Edgar Ribi, Ph.D., Robert F. Smith, Ph.D.
Rickettsial Diseases—Willy Burgdorfer, Ph.D., Robert L. Anacker, Ph.D., Richard A. Ormsbee, Ph.D.

National Institute of Arthritis, Metabolism and Digestive Diseases

J. E. Rall, M.D., Ph.D., Director of Intramural Research
John L. Decker, M.D., Clinical Director

Clinical Associates

The NIAMDD recruits about 10 new Clinical Associates each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Each Clinical Associate is assigned to one of the clinical branches or sections, within which he carries out both clinical work and laboratory studies. He is, in effect, an apprentice clinical investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The Associate is encouraged to choose his own problem for independent investigation, subject to the limitation that the facilities required for its successful pursuit and the technical advice and supervision necessary must be available to the branch or section in which he is working. In addition, he provides professional care for the research patients admitted to the service of his branch chief and assists in the work of that branch in the outpatient department. There is considerable variation among the branches of NIAMDD with respect to the proportion of the Associate's time required for patient care activities.

Clinical Associates of the Clinical Endocrinology, Diabetes, and Metabolic Diseases branches participate in a 3-year Inter-Institute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIAMDD Clinical Associates may also spend a third year in the Endocrinology Program.

Vacancies do not necessarily occur within each program area each year; the Program Area Selection Check List indicates the vacancies to be filled at any one time. The chiefs of branches or sections with openings and the Clinical Director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm his acceptance of the position to which he was assigned.

The Clinical Research Branches are listed below with the names of the permanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Dr. John L. Decker, Clinical Director, NIAMDD, Building 10, Room 9N222, NIH, Bethesda, Maryland 20014. Supplementary information sheets on each branch, together with selected bibliographic citations, are available on request.

Staff Associate in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment studying the epidemiology of chronic disease (diabetes, arthritis, cholelithiasis, etc.) among the Pima Indians of Arizona. In addition, clinical research opportunities are available in the Clinical Research Center of the Phoenix Indian Hospital. These Associateships begin after internship. Candidates interested in this possibility are encouraged to write Dr. Peter H. Bennett, Epidemiology & Field Studies Branch, NIAMDD, 1440 E. Indian School Road, Phoenix, Ariz. 85014, for more detailed information.

Research Associates

NIAMDD has four positions available each year for Research Associates. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During his stay here, each Research Associate will devote the larger part of his time to participation in laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should he elect a clinical area, he would not participate in clinical care of patients. The Research Associate, approximately 1 year prior to beginning, will visit NIAMDD to select the laboratory and preceptor with whom he wishes to work. Candidates desiring further information about the laboratories, staff, and bibliography can obtain this by writing Dr. J. E. Rall, Director of Intramural Research, NIAMDD, National Institutes of Health, Bethesda, Md. 20014.

Clinical Research Branches

ARTHRITIS AND RHEUMATISM BRANCH—Dr. John L. Decker

SECTION ON CONNECTIVE TISSUE DISEASE—Drs. John L. Decker, John H. Kilippel, Paul Plotz, and Alfred D. Steinberg

The pathogenesis of systemic lupus erythematosus (human and mouse models) is under study. Suppressor and activator lymphocyte isolation, development of stable immune complexes, and studies of anti-viral agents in the mouse model are in progress. Clinical work is on cytotoxic drugs in lupus nephritis, on survivorship variations with disease pattern, and on aspects of drug effects upon patients with lupus or rheumatoid arthritis.

SECTION ON CHEMICAL IMMUNOLOGY—Dr. Henry Metzger.

The section is involved in fundamental research on the structure and mechanism of immunoglobulins and their receptors on cells. Methods used include protein chemistry, immunochemistry, tissue culture, electronmicroscopy, and others.

SECTION ON HUMAN BIOCHEMICAL GENETICS—Drs. Elizabeth F. Neufeld and Raphael D. Camerini-Otero

Studies of a group of human genetic diseases cover basic aspects (e.g., research on those enzymes and mechanisms which are altered by the mutations) and practical applications (diagnosis and carrier detection, preparation of enzymes for replacement trials).

CLINICAL ENDOCRINOLOGY BRANCH—Drs. Jacob Robbins, Jan Wolff, Saul Rosen, Harold Edelhoch, and Bruce Weintraub

Activities range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid and polypeptide hormones. Laboratory research includes fundamental and applied protein chemistry, hormone actions, cellular control mechanisms.

CLINICAL HEMATOLOGY BRANCH—Dr. N. Raphael Shulman

Laboratory work concerns the biochemistry of blood coagulation, platelet physiology and metabolism, and various problems in the field of immunohematology. Examples of current work are: isolation and characterization of Factor VIII and platelet aggregating factor, studies of the mechanism of action of circulating anticoagulants, evaluation of platelet nucleotide metabolism with respect to platelet function, and analysis of molecular changes in prothrombin during its conversion to thrombin. Clinical work involves patients with hemorrhagic and immunologic disorders relevant to the laboratory studies.

DIABETES BRANCH—Drs. Jesse Roth, Phillip Gorden, Ronald Kahn, and Matthew Rechler

Attention is on peptide hormones, especially insulin, growth hormone, and insulinlike growth factors. Recent work has been largely on the interaction of the peptide hormones with their receptors on the surface membrane of target cells, with emphasis on situations where the concentration or affinity of the receptor changes in response to intracellular or extracellular events. A broad range of experimental approaches are used to explore these processes including cell culture, purification of hormones and of membrane components, and studies of rodents and people with a wide variety of insulin resistant conditions.

DIGESTIVE DISEASES BRANCH

SECTION ON GASTROENTEROLOGY—Drs. Jerry D. Gardner and Denis M. McCarthy

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunological processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology biochemistry and immunology.

SECTION ON DISEASES OF THE LIVER—Drs. Paul D. Berk and E. Anthony Jones

Hepatic transport processes are investigated by means of kinetic studies in patients, animals, isolated prefused livers, and subcellular preparations. Investigations of various approaches to the design of an artificial liver are actively pursued. Cellular immunology and the complement system are investigated in patients with primary biliary cirrhosis and chronic hepatitis. Studies of copper kinetics are being conducted in patients with increased hepatic deposition of copper. The metabolic behavior of alpha-1-antitrypsins of different molecular structure is being evaluated *in vivo* and *in vitro*. Emphasis is on the application of basic biochemical, biophysical, immunologic and mathematic techniques to clinical investigation.

METABOLIC DISEASES BRANCH—Drs. Gerald D. Aurbach and Stephen Marx

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone and calcitonin. The clinical program involves studies of patients with disorders of mineral metabolism. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is available for *in vitro* studies and is cryopreserved for a study of management of postoperative hypoparathyroidism with parathyroid autotransplantation.

PEDIATRIC METABOLISM BRANCH—Dr. Paul A. diSant' Agnese

Cystic fibrosis of the pancreas is the target of both laboratory and clinical work. Glycoproteins, polyamines, the circulating ''cystic fibrosis'' factor and other substances are analyzed for their possible relationship to sweat and saliva electrolyte abnormalities. Techniques used include amino acid analyses, automated ion exchange and thin-layer chromatography, radioisotope analyses by liquid scintillation counting and tissue culture. A variety of clinical aspects such as Vitamin E deficiency, the reninaldosterone axis, and cyclic nucleotides are studied and the course and complications of cystic fibrosis are documented.

PHOENIX CLINICAL RESEARCH UNIT—Dr. Peter H. Bennett

Diseases unique to or particularly prevalent among American Indians are studied.

Current investigations focus on diabetes, gallbladder disease and lipid disorders and include studies of insulin receptors, hormonal abnormalities in diabetic and prediabetic subjects, lipid and lipoprotein metabolism, and studies of biliary lipid metabolism and physiology in Southwestern American Indians. Investigations are carried out at the Phoenix Clinical Research Center, a 24-bed clinical research unit with full supporting laboratory facilities located within the Indian Health Service Referral Hospital in Phoenix, Arizona.

Basic Research Laboratories

MATHEMATICAL RESEARCH BRANCH—Dr. John Z. Hearon

LABORATORY OF NUTRITION AND ENDOCRINOLOGY—Dr. Martin Rodbell
  Section on Nutritional Biochemistry—Dr. John G. Bieri
  Section on Endocrinology—Dr. Robert O. Scow
  Section on Vitamin Metabolism—Dr. Bernard Kaufman
  Section on Developmental Biochemistry—Dr. Robert T. Simpson
  Section on Membrane Regulation—Dr. Martin Rodbell

LABORATORY OF BIOCHEMISTRY AND METABOLISM—Dr. G. Gilbert Aswell
  Section on Enzymes and Cellular Biochemistry—Dr. William B. Jakoby
  Section on Intermediary Metabolism—Dr. Yale J. Topper

LABORATORY OF EXPERIMENTAL PATHOLOGY—Dr. Robert Friedman
  Section on Molecular Pathology—Dr. George G. Glenner
  Section on Chemical Pathology—Dr. Robert Friedman
  Section on Biophysical Histology—Dr. Ned Feder
  Section on Cytogenetics—Dr. J. H. Tjio

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Dr. Herbert Tabor
  Section on Pharmacology—Dr. Herbert Tabor
  Section on Biochemistry—Dr. Victor Ginsburg
  Section on Biochemistry of Amino Acids—Dr. Simon Black
  Section on Biochemistry of Cell Regulation—Dr. Leonard Kohn

LABORATORY OF CHEMISTRY—Dr. Bernhard Witkop
  Section on Carbohydrates—Dr. C. Glaudemans
  Section on Medicinal Chemistry—Dr. Everette L. May
  Section on Biochemical Mechanisms—Dr. Louis A. Cohen
  Section on Metabolites—Dr. Bernhard Witkop
  Section on Microanalytical Services and Instrumentation—Dr. David Johnson
  Section on Pharmacodynamics—Dr. John W. Daly
  Section on Oxidation Mechanisms—Dr. Donald M. Jerina

LABORATORY OF PHYSICAL BIOLOGY—Dr. Richard J. Podolsky
  Section on Comparative Physiology—Dr. John B. Buck
  Section on Cellular Physics—Dr. Richard J. Podolsky

LABORATORY OF CHEMICAL PHYSICS—Dr. Edwin D. Becker
  Section on Molecular Biophysics—Dr. Edwin D. Becker
  Section on Physiology—Dr. Paul Altland
  Section on Spectroscopy and Structure—Dr. Elliot Charney
  Section on Membrane Biophysics—Dr. William A. Hagins

LABORATORY OF MOLECULAR BIOLOGY—Dr. Gary Felsenfeld
- Section on Metabolic Enzymes—Dr. Martin Gellert
- Section on Molecular Genetics—Dr. Jun-ichi Tomizawa
- Section on Physical Chemistry—Dr. Gary Felsenfeld
- Section on Molecular Structure—Dr. David R. Davies
- Section on Microbial Genetics—Dr. Robert Martin
- Section on Organic Chemistry—Dr. H. Todd Miles
- Section on Theoretical Molecular Biology—Dr. Terrell Hill

LABORATORY OF CHEMICAL BIOLOGY—Dr. Christian B. Anfinsen
- Section on Protein Chemistry—Dr. Christian B. Anfinsen
- Section on Protein Conformation—Dr. Hiroshi Taniuchi
- Section on Macromolecular Biology—Dr. Alan Schecter

LABORATORY OF BIOPHYSICAL CHEMISTRY—Dr. Harry Saroff
- Section on Bioenergetics
- Section on Macromolecules—Dr. Harry A. Saroff
- Section on Physical Biochemistry—Dr. Koloman Laki

National Institute on Aging

Intramural Research Program

Richard C. Greulich, Ph.D., Acting Scientific Director
Reubin Andres, M.D., Clinical Director

The Intramural Research Program of the National Institute on Aging is located at the Gerontology Research Center in Baltimore, Md.

The multidisciplinary program of the Center, located in a special research building on the campus of the Baltimore City Hospital, offers 2-year Clinical (primarily clinical research) and Staff (primarily basic research) Associate training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, associates may participate in clinical activities of the Baltimore City Hospital and the nearby John Hopkins Hospital.

In addition to the 2-year appointments, a 3-year program of clinical and research training in collaboration with the Division of Cardiology, Department of Medicine, Johns Hopkins University, the Department of Psychiatry, Johns Hopkins University, or the Department of Medicine, Baltimore City Hospital, is offered to a limited number of candidates. Under this program, the associate spends his first year in clinical training as a Resident Physician or Clinical Fellow in one of the above departments. The second and third years are spent in clinical or laboratory research on gerontology or geriatrics at the Center.

Associates participate in a seminar conducted by the staff of the Center which presents a comprehensive view of research in aging. Weekly research conferences are presented by members of the staff and invited lecturers.

In support of the programs the Center maintains extensive animal colonies to provide rats, mice, and house flies of known ages, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment. Computer facilities for electronic data processing are available at the Center. Instruction in the use of computers in laboratory research is provided. The library of the Center includes standard scientific journals as well as an extensive collection of the literature on aging research. The Center also has approved clinical research programs in which 650 male volunteers, aged 18–96, report to the Center regularly at 1–2 year intervals for 2½ days of intensive testing.

The Gerontology Research Center is composed of four branches:

LABORATORY OF CELLULAR AND COMPARATIVE PHYSIOLOGY (C. H. Barrows, Sc.D., Acting Chief). This laboratory is concerned with the effects of age in humans and other mammalian species. Currently, emphasis is placed on immunologic, biochemical, and genetic evaluations of cells of animals which differ genetically as well as those whose life span has been altered by dietary manipulation.

The research in nutritional biochemistry identifies the differences in the biochemical characteristics of cells in animals whose life span vary due to dietary manipulation. Emphasis is placed on the relationship among rates of enzymatic synthesis, age-associated changes in enzymatic activities and structure and diet. Morphological changes are examined by high resolution electron microscopy (transmission and scanning).

The research in immunology is under the direction of A. A. Nordin, Ph.D. and W. H. Adler, M.D. and is concerned with the development of reliable assays for the detection of the age-related immunodeficiency in human and laboratory animals. Both the decline of cell-mediated and humoral immunity as seen in aging are being investigated. The mechanism of this decline, the diagnosis of the deficiency, the correlation of a poorly functioning immune system with age-related diseases and the possibility of reversing the decline or overriding the deficiency are all actively pursued projects in this laboratory.

Research emphasizing a comparative cellular and molecular biological approach using animals genetically closely related to one another but having substantial differences in their natural life span potentials is under the direction of Richard G. Cutler, Ph.D. This program is focused on learning about the possible existence of primary aging processes and of mechanisms that may govern their rate of expression in man. Current research concerns age-dependent changes that occur at the genetic apparatus level and of protective and repair processes that may exist to govern its functional life span in the cell.

Research in mammalian cell biology, under the direction of Edward L. Schneider, M.D., is focused on studies of cell replication, repair of DNA damage, and nucleic acid metabolism in both human cells in culture and in living animal tissues. The effect of parental age on the production of genetically abnormal offspring is being examined in appropriate animal models.

CLINICAL PHYSIOLOGY BRANCH (Reubin Andres, M.D., Chief). This branch is primarily concerned with studies on physiological changes occurring during the entire adult age span. Studies include quantitation of age changes, elucidation of mechanisms underlying these changes, and the relation between aging processes and specific disease states.

The ENDOCRINOLOGY SECTION (Robert I. Gregerman, M.D., Chief) conducts studies on (1) the molecular bases of age-related changes of hormone responses, especially as related to the biochemistry of the adenylate cyclase system and hormone receptors, (2) aging and the endocrinology of the reproductive system, and (3) the enzymology and peptide chemistry of the renin-angiotensin system.

The CARDIOVASCULAR SECTION (Edward G. Lakatta, M.D., Chief) investigates cardiovascular hemodynamic function in man using noninvasive methods and in the rat and dog by a variety of experimental techniques. Studies on the effects of age on the biophysical properties of cardiac muscle are also conducted in animal models.

The METABOLISM SECTION (Reubin Andres, M.D., Chief) conducts research on the kinetics of glucose homeostasis and its endocrine control. Factors controlling insulin secretion, including gastrointestinal insulinotropic hormone, are quantified using the servo-control glucose clamp technique in man. Efforts are directed at the evaluation of normal physiology and changes with aging, obesity, diabetes, and other metabolic disorders.

The HUMAN PERFORMANCE SECTION (Arthur H. Norris, M.A., Chief). This section is responsible for a wide variety of studies on age changes in body composition, pulmonary and exercise physiology, and neuromuscular function.

LABORATORY OF BEHAVIORAL SCIENCES (Bernard T. Engel, Ph.D., Chief). This program includes studies of the effects of aging on motor behavior, perceptual skills, learning, memory, problem-solving ability, and personality characteristics. There are also studies on the interrelationships among aging and autonomic responses. The clinical applications of voluntary autonomic control are being investigated. Laboratory facilities exist for measuring cognitive and perceptual functions in man; psychophysiological responses in man; learning and motor behavior in rodents (including selected inbred strains of mice); learning, cardiovascular and neuropsychological responses in monkeys.

The LABORATORY OF MOLECULAR AGING (Bertram Sacktor, Ph.D., Chief) investigates mechanisms of the control of metabolism and of the expression of genetic information. The thrust of the research on metabolic processes is directed toward membrane biology. The problems and questions studied relate to: (1) the molecular organization of the membrane; (2) the role of the membrane in vectoral transport of small molecular species and proton-motive force; (3) the membranal reception of hormonal stimuli, the transduction and propagation of these stimuli; (4) the catalytic and integrative function of membranes; (5) the turnover of membranes; and (6) the failure to maintain membrane structure, leading to cell death. The thrust of the work on the propagation of genetic information is directed toward the interaction of metal ions with nucleic acids and proteins with the object of understanding these interactions in terms of biological function and particularly in the replication of DNA, transcription of RNA, and the synthesis of proteins.

Intramural Research Program

James B. Sidbury, M.D., Scientific Director
D. Lynn Loriaux, M.D., Ph.D., Acting Clinical Director

The NICHD had 8 associate positions available each year. The appointments are for two or three years. The specific programs are indicated below. More detailed description of specific programs is available on request.

The Reproductive Research program is approved for accreditation by the Endocrinology Boards. The pediatric component of the perinatal program includes developmental pharmacology, neonatology, and biochemical genetics. The trainee who selects the pediatric program will rotate on the infant and children's wards, participating in clinical research programs as well as providing the care on those wards. During the first year he will select the laboratory he wishes to work in for the subsequent two years. This permits the trainee to select the laboratory experience after more knowledgeable exposure. Completion of the PL-2 pediatric experience is required.

The LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY (Phillip G. Nelson, M.D., Ph.D., Chief) conducts electrophysiologic and biochemical studies of the neurobiological basis for short- and long-term interaction between nerve cells. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques. Combined molecular and behavioral methods are used in the analysis of experiential modification of brain function.

The SECTION ON BRAIN AND BEHAVIOR (David Symmes, Ph.D., Chief). Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed using microelectrode computer techniques. The focus of interest is in vocal communication among subhuman primates and possible relationships to human speech.

The SECTION ON FUNCTIONAL NEUROCHEMISTRY (Harold Gainer, Ph.D., Chief), conducts analysis of biochemical changes in identified neurons associated with electrophysiological and behavioral alterations. Specific neuronal protein synthesis and axoplasmic transport, glial-neuronal interactions, pacemaker activity, and neural peptides are studied.

The SECTION ON INTERMEDIARY METABOLISM (Gordon Guroff, Ph.D., Chief). This Section is involved in studies on the mechanism of action of enzymes of neurochemical interest, the biosynthesis and degradation of macromolecules in neural tissue, and the mechanism of action of nerve growth factor. Other studies concern the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation.

The SECTION ON NEUROBIOLOGY (Philip G. Nelson, M.D., Ph.D., Chief). Tissue cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied electrophysiologically and biochemically. Long-term interactions between neurons and between nerve and muscle are of particular interest.

The SECTION ON NEUROENDOCRINOLOGY (David C. Klein, Ph.D., Chief). Research activities involve environmental, pharmacological, developmental and biochemical factors critical to the metabolism and function of the pineal gland. Current studies on this model of neural and neuroendocrine regulation focus on the molecular mechanism involved in the trans-synaptic adrenergic-cAMP regulation of gene expression. In addition, control by the pineal gland of reproductive physiology is investigated.

The LABORATORY OF BIOMEDICAL SCIENCES (J. C. Robinson, M.D., Ph.D., Chief) conducts basic research in developmental enzymology and physiological controls.

The SECTION ON DEVELOPMENTAL ENZYMOLOGY (J. C. Robinson, M.D., Ph.D,, Chief). Primary interest centers on the identification and characterization of pregnancy-associated maternal blood plasma enzymes and proteins, the characterization of enzymes synthesized by the placenta, and an analysis of some of the factors involved in enzyme induction in the developing fetus.

The SECTION ON PHYSIOLOGICAL CONTROLS (Walter H. Glinsmann, M.D., Chief) is concerned with hormonal, neurotransmitter, and substrate regulation of cell function. Current studies focus on the role of phosphoproteins in the regulation of cellular metabolism and differentiation.

The LABORATORY OF MOLECULAR GENETICS (Philip Leder, M.D., Chief) consists of a group of scientists using the tools of molecular and cellular biology to answer questions about differentiation, development and the control of genetic functions in simple and complex organisms. The range of model systems under investigation includes bacterial and animal viruses, tumor cells, embryonic lens tissue as well as the differentiating hematopoietic and immune organ systems. Techniques employed range from bacterial, viral, cell culture methods to gene isolation and recombinant DNA technology.

RESEARCH SECTIONS AND SENIOR STAFF:

The SECTION ON GENE ORGANIZATION AND CONTROL—Edgar E. Hanna, Ph.D., Philip Leder, M.D., Judith G. Levin, Ph.D.

The SECTION ON MOLECULAR REGULATION—Michael Cashel, M.D., Ph.D., Robert Crouch, Ph.D.

The SECTION ON MOLECULAR STRUCTURE—Jacob V. Maizel, Jr., Ph.D.

The SECTION ON CELLULAR DIFFERENTIATION—Joram Piatigorsky, Ph.D.

The SECTION ON MICROBIAL GENETICS—Robert Weisberg, Ph.D.

The SECTION ON ANIMAL VIRUSES—Heiner Westphal, M.D.

The DEVELOPMENTAL PHARMACOLOGY BRANCH (Daniel W. Nebert, M.D., Chief) investigates the molecular mechanisms underlying genetic differences and environmental factors affecting drug metabolism. Interests of the Branch span from biophysical characterization of membrane-bound and cytosolic enzymes to use of mammalian model systems, especially the inbred mouse and rat, to projects in clinical pharmacology.

The SECTION ON PHARMACOGENETICS AND MOLECULAR TERATOLOGY (Daniel W. Nebert, M.D., Chief) is concerned with the development of methods *in vitro* and in cell culture for assessing and predicting teratogenic, toxic, mutagenic, or carcinogenic effects of exogenous or endogenous compounds in animal model systems and in man. Developmental curves and the expression of genes controlling drug-metabolizing enzymes are studied, and the transplacental inducing effect of drugs, chemical carcinogens, mutagens, and other environmental pollutants are investigated as possibly important factors in the etiology of birth defects. Within this section, Ida S. Owens, Ph.D., as head of a unit on drug-conjugating enzymes, explores mechanisms involved in the coordinate genetic control of certain inducible drug-metabolizing enzymes and the potential significance of this type of control in toxicity of certain drugs. Drug metabolism is examined in cell culture and mouse genetic model systems. Characterization of factors in human milk that produce jaundice beyond the newborn period is also under investigation.

The NEONATAL AND PEDIATRIC MEDICINE BRANCH (J. B. Sidbury, M.D., Acting Chief) conducts research on the diagnosis, treatment, and fundamental mechanisms of diseases of infants and children. Emphasized are inborn errors of metabolism, nutritional deficiency states, developmental and physiologic aspects of intestinal cells, congenital malformations, endocrine disturbances of children, and effects of disorders of maternal origin on the neonate.

The SECTION ON DEVELOPMENTAL BIOLOGY AND CLINICAL NUTRITION (James W. Hansen, M.D., Ph.D., Acting Chief). This section conducts research in nutrition, developmental endocrinology, and mineral metabolism in infants and children. Use of stable isotopes, mass spectrometry, computer modeling, radioactive tracer techniques, flameless atomic absorption spectrophotometry, and calcium electrode allow the detailed study of calcium, magnesium and trace element kinetics and metabolism in both children and laboratory animals, including non-human primates.

The SECTION ON HUMAN BIOCHEMICAL AND DEVELOPMENTAL GENETICS (Joseph D. Schulman, M.D., Chief) investigates various inborn errors of metabolism, especially disorders affecting the sulfur amino acids, and seeks improved understanding of the molecular basis of these diseases and new methods for diagnosis and treatment. Fetal metabolism of amino acids, amino acid transport, and developmental biochemistry are also areas of active investigation.

The SECTION ON DEVELOPMENTAL GASTROENTEROLOGY AND NUTRITION (Norman Kretchmer, M.D., Ph.D., Chief) The purpose of this section is to study the differentiation of the intestinal crypt cell. Elucidation of the mechanisms of intestinal proliferation may aid in the understanding of malabsorption states such as chronic diarrhea of infancy, short bowel syndrome, coeliac disease, and other states where the regeneration of the intestinal mucosa is of major concern.

The ENDOCRINOLOGY AND REPRODUCTION RESEARCH BRANCH (Kevin J. Catt, M.D., Ph.D., Chief) conducts an integrated program of clinical, biochemical, and biologic studies pertinent to encrinology and reproductive biology. The Branch accepts three Clinical Associates each year. During the first year, the Associate will rotate among the Endocrinology Branches of the NIH to gain a broad knowledge of clinical endocrinology. The next two years are spent primarily in laboratory investigation in collaboration with a senior investigator.

The SECTION ON HORMONAL REGULATION (Kevin J. Catt, M.D., Ph.D., Chief) places emphasis on the binding and effects of polypeptide hormones such as gonadotropins and angiotensin. Major effects include characterization and isolation of membrane receptors and analysis of the receptor-second messenger systems.

The DEVELOPMENTAL ENDOCRINOLOGY SECTION (D. Lynn Loriaux, M.D., Ph.D., Chief) examines the endocrine concomitants of growth, development, and differentiation. Current laboratory investigations include the mechanism and control of steroid biosynthesis, secretion, transport, and target tissue action. Of particular clinical interest are disorders of adrenal function, male and female infertility, and disorders of puberty and secondary sexual development.

The SECTION ON ENDOCRINOLOGY (Gary Hodgen, Ph.D., Chief) conducts basic research in reproductive endocrinology and in laboratory aspects of clinical investigation. Major emphasis is placed on non-human primates for studies of ovarian function and pregnancy and on the physiology and chemistry of gonadotropins.

The SECTION ON MOLECULAR STRUCTURE (Erhard Gross, Ph.D., Chief) conducts research on the analysis and synthesis of peptides with unique structural features.

Correlations between structure and biological activity are analyzed in hypothalamic releasing factors, chemotactic and ion-channel forming peptides, and peptides causing fetal resorption and inhibition of tumor growth.

The SOCIAL AND BEHAVIORAL SCIENCES BRANCH (Leon J. Yarrow, Ph.D., Chief) engages in research on cognitive, social, and motivational development. Studies in progress have concentrated on the first year of life. Current investigations are concerned with both methodological and theoretical issues regarding early environmental influences, the assessment of neonatal characteristics, the measurement of mastery behavior during infancy and the emergence of the special bond between mother and infant. Studies are focused on how specific early experiences are related individually and in interaction to the development of these characteristics. Research is also underway on reciprocal influences in parent-infant interaction, e.g., describing the interactions between the infant's early characteristics, parental characteristics, and parental relationships. A methodological study on the development and expression of attachment in several settings is being carried out.

National Institute of Dental Research

Marie U. Nylen, D.D.S., Dr. odont., h.c., Director of Intramural Research
Reuben P. Siraganian, M.D., Acting Clinical Director

The National Institute of Dental Research conducts research programs in laboratory, clinical and applied science, germane not only to dental health but also to the broader interests of biology and medicine.

Physicians are appointed for a 2-year period to the Institute's laboratory or clinical programs as Research or Clinical Associates. In general, three Research Associate and two Clinical Associate positions are available annually. Specific program areas, however, will not necessarily have vacancies for Associates in a particular year.

For the most part, dentists will be appointed for 2 years as Dental Clinical Associates, with a dual commitment to research and service as described on page 2. Dental graduates who possess specialized training and interests applicable to a particular research program of the Institute may also be considered for appointment as Staff Associates, with a full-time assignment to the appropriate laboratory or branch. The number of positions of this type to be filled will be determined solely according to programmatic need.

Minimum qualification for appointment as a Dental Clinical Associate is 1 year of accredited internship, or possession of equivalent advanced training beyond the dental degree. Dentists who have recently completed specialty training will be given particular consideration. Selection will usually be made one year prior to the effective date of appointment. Thus, for example, senior dental students who will enter an accredited internship July 1, 1977, are eligible to apply for an appointment commencing in 1978.

Brief descriptions of the program areas to which Associate appointments are made are provided in the following paragraphs. Additional information about specific programs may be obtained upon request to the Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, Md. 20014.

The LABORATORY OF BIOCHEMISTRY (Karl A. Piez, Ph.D., Chief) conducts programs in basic research covering a broad range of biochemical topics. The laboratory has as its objective the investigation of fundamental biochemical processes in normal and disease states.

There are two sections within the laboratory to which an associate may be assigned.

The PROTEIN CHEMISTRY SECTION (Karl A. Piez, Ph.D., Chief) is concerned with the chemistry, structure and biosynthesis of collagen, elastin, and the proteoglycans of connective tissue. Structure at the molecular level and the interactions that produce higher level tissue structure are determined by chemical, biophysical, and ultrastructural methods.

The ENZYME CHEMISTRY SECTION (John E. Folk, Ph.D., Chief) is studying the mechanism of action of enzymes using transglutaminases as models. These enzymes produce crosslinks in fibrin during blood clotting, in hair proteins, and in other biological situations. Protein chemical modification, synthesis of substrates, enzyme kinetics, and characterization of the products of crosslinking are used to elucidate the important aspects of enzyme structure and its relationship to catalytic activity.

The LABORATORY OF MICROBIOLOGY AND IMMUNOLOGY (Stephen E. Mergenhagen, Ph.D., Chief) has as its broad objective the elucidation of the role of microorganisms and immunological mechanisms in oral and systemic health and disease. The basic and clinical programs have application to medical and dental problems of cooperative research with other laboratories is conducted as required by the interdisciplinary nature of particular projects.

NIH Associates are assigned to one of four sections according to the interest of the candidate: Cellular Immunology (Joost J. Oppenheim, M.D., Chief), Humoral Immunity (Ann L. Sandberg, Ph.D., Chief), Clinical Immunology (Reuben P. Siraganian, M.D., Chief), or Microbiology (Charles L. Wittenberger, Ph.D., Chief).

Present projects in immunology encompass the role of cell-mediated immunity, immune complexes and their effector systems (e.g., complement, vasoactive amines, lymphokines) in acute and chronic inflammatory reactions ultimately related to periodontal diseases, oral mucosal diseases, tissue transplantation, and autoimmune diseases. The microbiological programs include studies on microbial determinants of oral and systemic diseases, bacterial metabolism and its regulation, microbial genetics and molecular biology, and taxonomy and ecology of the oral microbiota. Wherever possible fundamental approaches in these disciplines are translated into clinically-oriented or more applied projects through research protocols in clinical immunology as well as through collaboration with the National Caries Program of this Institute.

The LABORATORY OF BIOLOGICAL STRUCTURE (Rotating Acting Chiefs: E. D. Eanes, Ph.D.; A. R. Hand, D.D.S.; J. D. Termine, Ph.D.) is primarily concerned with structural parameters of normal and abnormal function as expressed at varying strata of biological organization, ranging from the subcellular to the organ level. Information is adduced from the application of biophysical and biochemical methods, techniques of experimental embryology, as well as from relevant tools of modern histology.

Research and Staff Associates are appointed to the Laboratory and are assigned by mutual agreement to a preceptor in the Molecular Structure Section (E. D. Eanes, Ph.D., Chief) or the Experimental Morphology Section (M. U. Nylen, D.D.S., Chief).

Currently the MOLECULAR STRUCTURE SECTION is engaged in studies on the crystal chemistry of calcium phosphates, the kinetics of mineral nucleation and crystal growth, calcification mechanisms, biochemistry of noncollagenous proteins in mineralized tissue and cell matrix interactions in endochondrial bone development. The interests of the EXPERIMENTAL MORPHOLOGY SECTION are divided into two principal areas: (1) the growth and differentiation of mineralized tissues, normal as well as abnormal, and (2) the structure and function of exocrine glands with emphasis on the salivary gland. Opportunities for cooperative research and training are offered in electron microscopy and diffraction, contact microradiography, x-ray diffraction, vibrational spectroscopy, phosphoprotein biochemistry and developmental embryology.

The LABORATORY OF DEVELOPMENTAL BIOLOGY (George R. Martin, Ph.D., Chief) conducts research in (1) normal and abnormal tissue development, particularly craniofacial development and the etiology of anomalies, and (2) on the chemistry, biosynthesis and degradation of oral and other connective tissues.

The CONNECTIVE TISSUE SECTION (George R. Martin, Ph.D., Chief) conducts research on the formation and degradation of connective tissue with particular emphasis on developing structures. It relates the properties of these components to normal and pathological processes.

The CRANIOFACIAL ANOMALIES SECTION (Robert M. Pratt, Jr., Ph.D., Chief) conducts research on both normal and abnormal aspects of craniofacial development. Malformations in these structures, similar to human anomalies, can be predictably produced by genetic and/or environmental manipulation in order to determine the molecular basis for the defects.

The NEUROBIOLOGY AND ANESTHESIOLOGY BRANCH (Ronald Dubner, D.D.S., Ph.D., Chief) is concerned with the elucidation of basic mechanisms of oral-facial sensation with particular emphasis on pain sensation, and with the development and application of new methods of pain control. Fundamental research on peripheral and central nervous system mechanism of oral-facial sensation is conducted by the NEURAL MECHANISMS SECTION (Ronald Dubner, D.D.S., Ph.D., Chief). The primary objective of this research group is to correlate behavioral responses to noxious and non-noxious thermal stimuli in the monkey with neuronal structure and function at various levels of the trigeminal system. A multidisciplinary approach is employed and includes the following research activities: (1) electrophysiological studies of the response of single trigeminal nerve fibers and trigeminal brain stem neurons to noxious and innocuous thermal and mechanical stimuli applied to the oral-facial region of monkeys; (2) neurocytological studies of the receptor, primary afferent, and brain stem organization and the trigeminal system in cat and monkey utilizing light- and electron-microscope techniques; and (3) behavior studies involving pain and temperature discrimination in monkeys trained to avoid potentially noxious or noxious stimuli applied to the face. The NIDR computer system is utilized for data analysis in the physiological experiments and provides stimulus control in behavioral and combined behavioral-electrophysiological experiments. On-going behavioral and psychophysical studies involving human subjects are concerned with (1) the development and evaluation of new methods of measuring the sensory and affective components of pain (2) the evaluation of pharmacological and non-pharmacological methods of pain contol.

Applicants for positions in this section should have special training and experience in neurophysiology, neurocytology, experimental psychology, or computer technology.

Clinical research on new methods of pain control is conducted by the ANESTHESIOLOGY SECTION (Edward J. Driscoll, D.D.S., Chief). The research objectives and activities of this group include physiological, pharmacological, and psychological studies of the effects and efficacy of new pharmacological agents utilized in the control of pain in dental patients.

It would be advantageous for applicants for positions in this section to have some training and experience in anesthesiology, pharmacology or psychology.

The LABORATORY OF ORAL MEDICINE (Abner Louis Notkins, M.D., Chief) conducts basic and clinical research on diseases of the oral cavity. The program is highly interdisciplinary with emphasis on virology, oncology, and endocrinology. The staff includes people trained in medicine, dentistry, and the basic sciences. Present research projects include factors responsible for recurrent and persistent viral infections (e.g., herpes viruses), cellular immunity in viral infections, virus-induced immunopathology, the etiology of various dermatologic disorders including aphthous ulcers, and the role of viruses and other factors in diseases of the exocrine glands (e.g. Sjogren's syndrome, pancreatitis, salivary gland tumors) and endocrine glands (e.g., diabetes mellitus).

The CLINICAL INVESTIGATIONS BRANCH (Richard L. Webber, D.D.S., Ph.D., Chief) is concerned with clinical research of dental interest ranging from descriptive analyses involving the oral and pharyngeal tissues to the study of technical factors limiting diagnostic performance obtainable from radiographs. The emphasis is on establishing solid theoretical bases for improving diagnostic procedures as well as systematic documentation of clinical observations of various functional defects involving oral and related structures. As a result, new analytical tools and techniques are created and implemented in studies directed toward better understanding of a variety of dental disorders both developmental and degenerative. These include new schemes to analyze the shape of developing structures and a variety of image processing techniques intended to improve diagnostic accuracy obtainable from visual displays. The Branch is uniquely suited to these activities by virtue of the integrated efforts of a multidisciplinary staff. Expertise is complementary including technical competence in computer science and bioengineering as well as broad clinical experience. Ready access to a variety of research patients and professional personnel in the Clinical Center provides convenient opportunities for clinical demonstration of promising theoretical concepts and bases for potential application of new ideas.

The ORAL PHARYNGEAL DEVELOPMENT SECTION (James F. Bosma, M.D., Chief) is concerned with investigations of the development of form and of respiratory and feeding functions in normal and in impaired infants and children. Study methods commonly include standard and cephalometric roentgenography, cinephotography, and speech recording. Basic anatomic studies are an integral part of the work of this Section. Particular efforts are made to adapt familiar study techniques and therapies to patients severely handicapped by anomaly or by neurologic impairment.

The CLINICAL DENTAL SERVICES SECTION (John Folio, D.D.S., Acting Chief) has as its prime function the dual responsibility of providing dental care to the NIH-wide research patient population as well as of providing facilities and supportive activity to all intra-Institute clinical programs. This patient exposure provides a unique opportunity for gaining experience in the observation, treatment, and study of orofacial problems related to a variety of systemic disease. All Dental Clinical Associates are assigned to this Section administratively so as to facilitate their service-related activities. However, an individual program is arranged for each associate in order that he may also pursue effectively his clinical and/or basic research interests. This Section reports directly to the Clinical Director.

The DIAGNOSTIC METHODOLOGY SECTION (Richard L. Webber, D.D.S., Ph.D., Chief) undertakes a variety of research activities which include development of new diagnostic systems based on the application of specific analytical tools, including information theory, signal detection theory, and image processing by computer. Controlled psychophysical studies involving clinicians and lay personnel as subjects are used to test prototype systems in terms of clinically meaningful measures of diagnostic performance.

In addition to analysis and modeling of diagnostic systems, the Section also investigates new methods for quantitatively describing morphologically meaningful data via new geometric concepts. Opportunities for technically-oriented associates of all types, therefore, exist within the scope of interest encompassed by this Section.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D., Director

General

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biological factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods; the interaction of multiple agents resulting in enhanced effects; and the modifying effects of variable physical and biological states within man on susceptibility to and course of disease induced by these agents.

There is no single discipline that is unique or specific for the study of environmental health problems. Rather, the distinctive requirement for such research involves the application of a spectrum of skills including biology, biochemistry, bioengineering, biometry and epidemiology, chemistry, pathology, genetics, pharmacology, physics, toxicology, and veterinary sciences.

Location

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, N.C. The National Institute of Environmental Health Sciences is the only one of the 13 Institutes comprising the National Institutes of Health located away from the Bethesda, Md., campus.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University at Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, in seminars, and in other scientific and professional activities associated with the universities.

Staff Associates

Staff Associates will work at the National Institute of Environmental Health Sciences under the direction of Dr. David P. Rall, Director, and a Branch Chief in the Institute. Each associate will work directly under a senior scientist in an area of research chosen by the associate and the Institute.

The LABORATORY OF PHARMACOLOGY (James R. Fouts, Ph.D., Acting Chief) studies the toxic effects on mammals and marine species of low level and/or chronic exposure to environmental constituents or contaminants. Interactions (upon or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently underway include: toxication-detoxication systems in liver, lung, skin and gut—effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in lung and liver; interaction of chemicals at sites of and kinetics of chemical distribution, storage, metabolism, and release—especially in the isolated perfused lung and liver, species differences in xenobiotic disposition and metabolism, pharmacokinetics of pollutant disposition and studies on formation and metabolism of reactive metabolities of hydrocarbons in various marine species; purification and comparison of components of toxication-detoxication systems in various organs; changes in lung components (lipids, proteins, enzymes) as markers of disease or early damage by toxicants, including effects on synthesis and release of lung lipids (surfactant and prostaglandins); incorporation of chemicals into tissue proteins and enzymes and possible importance of these reactions to prolonged tissue storage or allergic reactions to chemicals.

The LABORATORY OF PHARMACOLOGY works extensively with other branches, Institutes and university departments; for example, our researchers in pharmacokinetics collaborate with Environmental Biometry, Environmental Biology and Chemistry, and Environmental Mutagenesis; developmental pharmacology with Environmental Toxicology; toxication-detoxication systems and marine pharmacology with Environmental Mutagenesis, Laboratory of Chemistry, NIAMDD; lung pharmacology and biochemistry with the Department of Medicine, Duke University.

The LABORATORY OF ENVIRONMENTAL MUTAGENESIS (H. V. Malling, Ph.D., Acting Chief) is responsible for the development of better methodology to test environmental chemical pollutants for mutagenic and carcinogenic activity as well as to monitor the human population to determine whether there is a change in the genetic load. In the first area, research currently underway includes investigation of the role of defective repair systems on inactivation and mutation-induction at specific gene loci, development of test systems in mammals to assay the effects of mutagens on the production of chromosome aberrations and gene mutations *in vitro* and *in vivo*, development of test systems to determine the genetic effect of airborne mutagens as well as the mutagenic effects of chemical carcinogens.

In the second area, method development is focused both on monitoring somatic mutations in peripheral blood cells and in skin fibroblasts, as well as on the detection and measurement of germinal mutations utilizing electrophoretic serum protein variants.

The techniques utilized in the investigations include: manipulation of mutagenic and carcinogenic agents, genetic analysis of microbial organisms, cytochemistry, mammalian tissue culture, autoradiography, cytogenetics, chromatography and ultracentrifugation, and electrophoresis.

The LABORATORY OF ENVIRONMENTAL TOXICOLOGY (Robert L. Dixon, Ph.D., Chief). Scientific efforts are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on the following tasks: (1) Determine mechanisms of teratogenesis using *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; (2) maintain an international teratology information center (ITIC); (3) assess environmental agents for their teratogenic potential; (4) study the molecular mechanisms underlying cellular differentiation; (5) evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; (6) understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; (7) determine the possible gestational origin of subtle toxic effects which do not become apparent until later in life; (8) define the effect of environmental agents on oogenesis and spermatogenesis; (9) examine the behavioral and neurological consequences of exposure to environmental substances; (10) develop preclinical predictors of toxicity using *in vitro* cells and tissues, lower animals, and biochemical test systems; (11) conduct studies focused at specific target organs to detect early or relatively low levels of toxicity and extrapolate these laboratory data to man.

The ENVIRONMENTAL BIOMETRY BRANCH (David G. Hoel, Ph.D., Chief). The mission of the Branch is to provide biometrical support for the NIEHS program by employing mathematical and statistical techniques to determine the biological effects of chemical, physical, and biological agents present in the environment. This is accomplished by incorporating in the Institute program statistical principles of experimental design, sampling, and data analysis for both laboratory and epidemiological studies, as well as mathematical analyses of biological systems. Mathematical and statistical procedures are applied and, when necessary, developed to determine the distribution and to estimate the rates of environmentally related diseases among populations, test hypotheses and study the interactions of environmental agents from multi-factor laboratory experiments, and develop mathematical models for describing and predicting biological responses to environmental agents. The Branch also provides computer support which ranges from the development of information retrieval and inventory maintenance systems to the simulation of complex biological models. In order to accomplish the mission of the Biometry Branch the following areas of activity are identified: (1) Analytical Statistics, (2) Epidemiology, (3) Mathematical Statistics, (4) Biomathematics, (5) Computer Programming, and (6) Data Processing.

The ENVIRONMENTAL BIOPHYSICS BRANCH (Colin F. Chignell, Ph.D., Chief) is involved in several studies on the biological effects of physical factors in man's environment. At present, the programs concentrate on biological effects of microwave radiation and noise singly and in combination with other factors. Microwave effects on reproduction and nerve functions (both isolated nerves and activities of the central nervous system as reflected in behavior) are under study. Noise effects on various inner ear functions are being studied in combination with ototoxic drugs and heavy metals. Newer methods have been developed for quantifying microwave doses and for studying sound effects on inner ear physiology and biochemistry. This development of methods and application of biophysical techniques to studies of environment-caused injury is an important aspect of the Branch programs.

The ENVIRONMENTAL BIOLOGY AND CHEMISTRY BRANCH (John A. Moore, D.V.M., Chief) maintains collaborative support laboratories in the disciplines of chemistry, inhalation toxicology, comparative pathology, immunology, and veterinary medicine, and plans and conducts research appropriate to the functions of Branch laboratories. Current research programs include studies on the effect of environmental chemicals on immune competence and pulmonary structure and function; characterization of the toxic effect of the chlorinated dibenzodioxins, dibenzofurans, and polychlorinated biphenyls; development of immunoassay methods; and instrumental methods, particularly mass and magnetic resonance spectrometric techniques to identify environmental chemicals and their transformation products.

National Institute of General Medicine Sciences

Byron B. Clark, Ph.D., Director of the Pharmacology Research
Associate Program

Pharmacology Research Associates

This Institute has positions available each year for Pharmacology Research Associates. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of the National Institutes of Health, under the Pharmacology Research Association Program.

The program is directed to those who have already made a commitment in pharmacology by training or research in the field.

Associates will study principles of pharmacology and toxicology and the application of physical and chemical concepts to pharmacology. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also available. During their tenure, Pharmacology Research Associates devote the larger portion of their time to laboratory research in the biomedical sciences, with no clinical responsibilities.

A special option in clinical pharmacology is also available to selected Pharmacology Research Associates with a medical background. Detailed information on this option may be obtained from the Pharmacology Research Associate Program.

The objective of the Program is to develop leaders in pharmacology research for key positions in academic, industrial, and governmental research laboratories.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance both the work in progress and the competence of the prospective independent investigator. Preceptors and Research Associates are matched by a mutual selection procedure after personal interviews.

Associate candidates include those who will have received either the Ph.D. or M.D. degree and have research experience in pharmacology or toxicology. They may also include those with research experience in a related area but who wish to further their development in pharmacology. M.D. candidates may use this opportunity to further their training in basic pharmacological research in preparation for a career in clinical pharmacology or a related discipline. Each of the following Institutes of the National Institutes of Health participates in the Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

National Cancer Institute

LABORATORY OF CHEMICAL PHARMACOLOGY—Richard H. Adamson, Ph.D.

The general areas being studied include: (1) the physiological disposition of antitumor agents; (2) structure-activity relationships (SAR) of anti-tumor agents; (3) new approaches to cancer chemotherapy and therapeutics in general, including studies with polymers and the nature of drug receptors; (4) comparative pharmacology; (5) induction of tumors in nonhuman primates with carcinogens and/or virus and chemotherapy of these tumors.

LABORATORY OF CHEMICAL PHARMACOLOGY—Snorri S. Thorgeirsson, M.D., Ph.D.

This Section on Biochemical Pharmacology is conducting studies on (1) the relationship between mutagenic and carcinogenic effects of drugs and foreign compounds, with emphasis on antitumor agents, (2) the mechanism of chemically induced cancer, with major emphasis on metabolic activation of chemical carcinogens and the genetic control of tumor initiation, (3) cell differentiation, both the mechanism of transformation (viral and chemical) and "redifferentiation" of already transformed cells with potentially therapeutic agents, and (4) clinical pharmacology, emphasis on pharmacokinetics, antitumor agents and drug toxicity.

LABORATORY OF CHEMICAL PHARMACOLOGY—Daniel S. Zaharko, Ph.D.

The Pharmacokinetics and Pharmacodynamics Section is involved with pharmacological investigations with cancer chemotherapeutic agents. Research efforts are currently directed towards altering the selectivity of known anticancer drugs by linking them to synthetic polymers and by using them in conjunction with normal intermediary metabolites such as nucleosides, amino acids or vitamins. Most studies are carried out in rodent species and involve pharmacokinetics, radioactive tracers, *in vitro* enzyme inhibition and tumor growth inhibition.

The research interests of this section are: (1) relationship between pharmacokinetics and drug effects; (2) biochemical selectivity of anticancer agents in different organs and tissues; and (3) the transport and role of nucleosides in whole animal biochemical balance.

LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY—David G. Jones, M.D., Ph.D.

Research is carried out on the pharmacology of cancer chemotherapeutics and related agents, and includes studies on the mode of action, physiological disposition and metabolism of this group of drugs. Of special concern are agents which act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the methotrexate: dihydrofolate reductase and 5-FdUMP:thymidylate synthetase interactions. Other areas of investigation include the role of enzyme induction in drug resistance; the effects of inhibition and enhancement of rates of drug metabolism on pharmacological activity; the physiological disposition of the rifampicin group of DNA- and RNA-polymerase inhibitors; and the role of the hepatic metalloflavoprotein aldehyde oxidase in the metabolism of N-heterocyclic compounds.

LABORATORY OF TOXICOLOGY—Theodore E. Gram, Ph.D.

The general area of research is in the factors which contribute to the termination of drug action, including metabolism and biotransformation of drugs and other xenobiotics, and enzymatic mechanisms controlling drug oxidation and conjugation in both hepatic and extra-hepatic tissues. Other areas of interest are the effects of biologically active antineoplastic agents on the metabolism of other drugs and the possible effects of enzyme induction or inhibition on the biological activity of oncolytic agents. In addition, work is underway in the area of drug-induced pneumotoxicity. A number of oncolytic drugs, including bleomycin, busulfan, methotrexate, and other drugs and xenobiotics induce a progressive pulmonary fibrosis in animals and in man which terminates in death due to pulmonary insufficiency. Studies are being started to investigate the pathologic insults involved at stages prior to actual increases in pulmonary collagen biosynthesis and the possibilities of arrest, reversibility, or even prophylaxis of this life threatening problem.

CHEMISTRY BRANCH—Harry V. Gelboin, Ph.D.

Research is being conducted on the molecular biology of microsomal enzyme regulation. Cell culture systems are used to study the mechanism of enzyme induction, the hydroxylation of polycyclic hydrocarbons, and the relationship of the microsomal enzyme system to drug action and carcinogenesis.

LABORATORY OF EXPERIMENTAL CHEMOTHERAPY—Abraham Goldin, Ph.D.

The program is concerned with the investigation of the mode of action of anticancer agents. Areas of investigation include: drug action in relation of cell cycle kinetics; metabolite-antimetabolite interrelationships in chemotherapy; combination chemotherapy with reference to drug potentiation and therapeutic synergism; adjuvant and immunochemotherapy; mechanisms and therapy of tumor cell resistance to drugs; tumor invasiveness and metastasis; structure-activity relationships of antitumor agents; chemotherapy of transplantable, carcinogen and viral induced, and spontaneous tumors; molecular biological and pharmacological investigation of the mechanism of action of antitumor agents. The laboratory program is closely related to clinical interests, and an attempt is made to establish therapeutic principles for transference to clinical chemotherapy.

LABORATORY OF MEDICINAL CHEMISTRY AND BIOLOGY—Marco Rabinovitz, Ph.D.

Investigations in this laboratory are concerned with the characterization of structures and functions of cells which contribute to their resistance to selected cancer chemotherapeutic agents. Analytical procedures are devised to study sensitive and resistant cell lines with regard to receptor sites and agent metabolism. Such information permits the introduction of pharmacological and nutritional regimens to counteract or augment the observed sensitivity or resistance.

The laboratory operations include tissue culture, use of tumor-bearing animals, radioactive tracer techniques, and the synthesis of appropriately modified agents or synergists.

National Institute of Dental Research

LABORATORY OF DEVELOPMENTAL BIOLOGY AND ANOMALIES—George R. Martin, Ph.D.

Individuals in this laboratory are studying the steps in normal and abnormal development. THE CONNECTIVE TISSUE SECTION emphasizes studies on the formation of these tissues. The SECTION ON CRANIOFACIAL ANOMALIES uses drug induced abnormalities to probe normal development.

National Institute of Mental Health

LABORATORY OF CLINICAL SCIENCE—Julius Axelrod, Ph.D.

The SECTION ON PHARMACOLOGY is engaged in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of drugs, biogenic amines, and enzymes; the distribution and metabolism of drugs, the isolation and characterization of enzymes involved in drug and biogenic amine metabolism. In addition, the laboratory is engaged in examining control mechanisms of the biochemistry of the pineal gland and biological rhythms.

LABORATORY OF CLINICAL SCIENCE—David M. Jacobowitz, Ph.D.

The SECTION ON HISTOPHARMACOLOGY is involved with studies of monominergic nerves (noradrenergic, dopaminergic, serotonergic), cholinergic nerves, and gabaminergic nerves in the brain and the peripheral autonomic nervous system. A multidisciplinary approach is used to correlate localization of central monominergic and cholinergic nerves with function. Histochemical, biochemical, and behavioral studies are currently underway. Using the catecholamine histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions is used to correlate changes in neuronal function with various parameters of behavior. Measurements of associated neuronal amines and enzymes are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a micropunch method and radioisotopic assays. Immunofluorescence methods are being used to study the localization of various enzymes in nerves. The growth of nerves is also studied using tissue and organ cultures.

LABORATORY OF CLINICAL SCIENCE—Irwin J. Kopin, M.D.

The research efforts of the SECTION ON MEDICINE are centered around the study of biochemical and physiological effects of drugs and toxins which alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes which control their synthesis in both the central and peripheral nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures.

Procedures are developed for application to clinical studies to evaluate neurotransmitter and neuroendocrine function in human subjects with various neuropsychiatric disorders during administration of psychoactive drugs. Plasma, urine, and CSF are analyzed for various drugs, amines, and metabolites, and their rates of utilization or synthesis determined using radioimmunological, enzymatic, or mass spectroscopic techniques.

LABORATORY OF PRECLINICAL PHARMACOLOGY—Erminio Costa, M.D.

This laboratory conducts a program of research in neurochemistry and neuropharmacology to elucidate the molecular nature of the mechanisms whereby various psychoactive drugs affect various neuronal systems. Current research includes: (1) the molecular regulation of postjunctional receptors with particular regard to the biochemical reactions occurring at the neuroeffector junction in response to the release from nerve terminals of catecholamines, serotonin, GABA, acetylcholine, and polypeptides which function as putative neurotransmitters; (2) the molecular nature of short term regulation of rate-limiting enzymatic reactions controlling the dynamic equilibrium of neuronal monoamines at synapses; (3) the regulation of acetylcholine metabolism as it relates to changes in neuronal function; (4) the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin, and GABA by mass fragmentography and to study drug actions at the synaptic level; (5) the role of cyclases, phosphodiesterases, phosphoprotein phosphatases, and protein kinase activation and translocation in the trans-synaptic regulation of gene expression in postsynaptic cells.

LABORATORY OF NEUROCHEMISTRY—Seymour Kaufman, Ph.D.

The main effort of the laboratory is concerned with the study of a group of enzymes that are involved in the oxidative metabolism of the aromatic amino acids. These enzymes include phenylalanine hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, and dopamine β-hydroxylase. These enzymes play unique roles—either directly or indirectly—in the normal development and functioning of the central nervous system. Phenylalanine hydroxylase, for example, occurs only in the periphery but its lack, as in the disease phenylketonuria, affects exclusively the CNS. The other enzymes catalyze key reactions in the biosynthesis of neurotransmitters, dopamine, norepinephrine and serotonin. One of the goals is to understand how the properties of these enzymes—catalytic, physical, and regulatory—determine their activity within the cell. The regulatory properties of these enzymes are being examined at various levels of tissue organization and include studies with highly purified enzymes, as well as those with cell suspensions, tissue slices and whole animals. One of the areas of current emphasis is the study of aspects of the enzymology of phenylketonuria and its variants in cultured fibroblasts.

LABORATORY OF CEREBRAL METABOLISM—Louis Sokoloff, M.D.

The Laboratory of Cerebral Metabolism carries out a broad program of investigations on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the central nervous system. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones, which play important physiological roles in CNS function. Present emphasis is on the mechanism of action of thyroid hormones, not only on the maturation of the nervous system, but also on metabolic processes in all susceptible tissues. A method has recently been developed in this laboratory which permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiological and pathological states.

LABORATORY OF GENERAL AND COMPARATIVE BIOCHEMISTRY—Werner A. Klee, Ph.D.

The major emphasis of our current program is directed towards the elucidation of the mechanism of action of opiates and the peptides which normally interact with opiate receptors. Included in this program are studies on the isolation and characterization of opiate receptors, of endogenous morphine-like factors, and of the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in tissue culture, are aimed at understanding narcotic tolerance and dependence as well as analgesia and euphoria in biochemical terms. The relevance of this work to the action of other CNS active drugs and to normal brain function is also being explored.

LABORATORY OF NEUROPHARMACOLOGY—Forrest F. Weight, M.D.

The research investigations in this laboratory have been on the pharmacology of single neurons and synapses in the central and peripheral nervous system. Recently this has included the role of cyclic nucleotides in synapic function. The research techniques offered are: (1) extracellular iontophoresis (microelectrophoresis) of drugs and chemicals to single neurons, (2) intercellular recording from single neurons, (3) intracellular iontophoresis of drugs and chemicals, (4) intracellular pressure injection of drugs and chemicals, (5) biophysical methods (such as conductance change and reversal potential) of investigating the mechanism of a drug's action on a neuronal membrane, and (6) extracellular ion changes to study the nature of permeability change of the membrane produced by a drug.

LABORATORY OF PRECLINICAL PHARMACOLOGY—N. H. Neff, Ph.D.

The section on biochemical pharmacology is concerned with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine containing neuron. Current studies are directed towards: (1) characterization of enzymes involved in amine metabolism; (2) biochemical evaluation of receptor responses; (3) evaluation and the mechanism of action of drugs that alter neuronal function; and (4) the possible role of the biogenic amines in various disease states.

National Institute of Arthritis, Metabolism, and Digestive Diseases

LABORATORY OF CHEMISTRY—John W. Daly, Ph.D.

The SECTION ON PHARMACODYNAMICS is engaged in research on the formation, degradation, and role of cyclic nucleotides in the central nervous system. The interrelationships between functional states of central neuronal networks and the responsiveness of cyclic nucleotide-generating systems to specific agents such as catecholamines, serotonin, histamine, adenosine, glutamate, GABA, etc.; the physiological role and mechanism of action of adenosine and membrane depolarization in regulation of cyclic AMP formation; and the morphological entities in brain slices associated with cyclic nucleotide formation in response to specific agents represent some aspects of this research.

ARTHRITIS AND RHEUMATISM BRANCH—Elizabeth Neufield, Ph.D.

Research is in the general area of human biochemical genetics, studied in cell culture. Of immediate interest are disorders of enzyme localization. For instance, in I-cell disease many hydrolytic enzymes are extracellular instead of intralysosomal. Such mutations lead to an understanding of the normal mechanism for packaging enzymes in their appropriate organelles.

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Herbert Tabor, M.D.

The work is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biological materials, and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Future work will be directed, in part, toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (e.g., enzyme characterization, baceteriophage, nucleic acid chemistry, isotopic and nonisotopic synthesis). The amino acid studies are concerned with the induced enzymes involved in histidine degradation, and their use as tools in studying induction, repression, and enzyme mechanisms. Other work in the laboratory includes studies on control mechanisms for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability.

LABORATORY OF BIOCHEMICAL PHARMACOLOGY—Loretta Leive, Ph.D.

This laboratory investigates the structure, assembly, and function of membranes. One area of study is the mechanism whereby gram-negative organisms resist drugs that attack gram-positive organisms. It was found that the gram-negative outer membrane excludes these drugs, and that the lipopolysaccharide of the membrane participates in this barrier function. Treatments that increase permeability and mutants altered in outer membrane components or permeability are being used to analyze the mechanisms involved. This research may suggest ways of increasing drug sensitivity in gram-negative organisms. Another area of study concerns mechanisms by which membranes assemble. The outer membrane appears heterogeneous, with areas specialized for insertion of new molecules, and the rates and mechanisms of insertion and rearrangement are being studied. These studies, in a system susceptible to genetic manipulation and with a relatively simple membrane, may help elucidate such properties, which are basic to membranes in general.

National Heart, Lung, and Blood Institute

MOLECULAR DISEASE BRANCH—W. French Anderson, M.D.

The SECTION ON MOLECULAR HEMATOLOGY investigates the mechanism and regulation of hemoglobin biosynthesis. Studies include the isolation and characterization of animal and human messenger RNA for hemoglobin, cell-free protein-synthesizing systems, the mechanism of initiation of protein synthesis, RNA transcription, cell fractionation, tissue culture of bone marrow cells, somatic cell hybridization, and patient investigations. Under direct investigation are the thalassemias, hemoglobinopathies, and other types of hemolytic anemias.

CARDIOLOGY BRANCH—Stephen E. Epstein, M.D.

The research objectives of this branch are oriented primarily toward an elucidation of the physiological and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacological interventions on the heart and peripheral circulation. Projects include pharmacologic, physiologic, and biochemical studies in man, intact animals, and smooth muscle cells grown in culture. Major emphasis is on the study of (1) the mechanisms responsible for arrhythmias and myocardial cell-death in acute myocardial infarction and their prevention, and (2) an understanding of the physiological and biochemical factors stimulating the atherosclerotic process.

LABORATORY OF CHEMICAL PHARMACOLOGY—James R. Gillette, Ph.D.

The SECTION ON DRUG-ENZYME INTERACTION studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objectives has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal level.

LABORATORY OF CHEMISTRY—John J. Pisano, Ph.D.

The SECTION ON PHYSIOLOGICAL CHEMISTRY, LABORATORY OF CHEMISTRY, studies normal and pathological states in man at the molecular level. Under investigation are the prostaglandins, neuroactive and vascoactive peptides (e.g., bradykinin and angiotensin), precursor proteins of the peptides and the enzymes involved in their biosynthesis and degradation. Modern analytical techniques such as gas chromatography, high performance liquid chromatography, affinity chromatography, mass spectrometry and radioimmunoassay are commonly used. Research is currently directed to the study of hypertension, coagulation, and fibrinolysis, micro methods for the detection of polypeptides and analysis of their amino acid sequence, and the discovery of naturally occurring biologically active peptides.

HYPERTENSION-ENDOCRINE BRANCH—Walter Lovenberg, Ph.D.

The research of the SECTION ON BIOCHEMICAL PHARMACOLOGY is directed toward an understanding of mechanisms and regulation of monoamine neurotransmitter synthesis and the relationship of monoaminergic systems to specific diseases. Some of our current projects are: (1) molecular mechanisms of short- and long-term regulation of tyrosine hydroxylase activity; (2) chemical, structural and biosynthetic studies on dopamine-β-hydroxylase; (3) molecular events in the transduction of nerve impulses into changes in target cell proteins and enzyme levels; (4) the mechanism and regulation of serotonin synthesis in the CNS; (5) *in vivo* and *in vitro* studies on the mechanism of centrally active drugs; (6) the role of central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields including pharmacology, enzymology, protein chemistry, and molecular biology.

LABORATORY OF BIOCHEMICAL GENETICS—Marshall Nirenberg, Ph.D.

The SECTION ON MOLECULAR BIOLOGY is conducting studies on clonal cells derived from the nervous system including those that are of normal and neoplastic origin as well as somatic cell hybrids. The objectives are to identify the molecules and the reactions that enable cells to communicate with each other, via synaptic junctions, and to investigate the problem of how genes determine neuron sequence as neurons are assembled into circuits during embryonic development. Work would involve predominantly biochemistry, mammalian cell cultures, cyclic nucleotide enzymology, cell receptors, and enzymes of neurotransmitter metabolism.

HYPERTENSION-ENDOCRINE BRANCH—Harry R. Keiser, M.D.

The SECTION ON EXPERIMENTAL THERAPEUTICS offers a spectrum of research opportunity ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins, and catecholamines conducted both in man and in experimental animals. Other current studies encompass disorders of serotonin and histamine.

LABORATORY OF BIOCHEMICAL GENETICS—Alan Peterkofsky, Ph.D.

The SECTION ON MACROMOLECULES is currently concentrating on studies of cellular control mechanisms. The major focus of interest at present is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells. The current information suggests that cyclic AMP concentrations in *E. coli* are controlled by cellular metabolites by a mechanism similar in some respect to that by which hormones affect cyclic AMP levels in many mammalian cells. Another current area for study involves the mechanisms of some unusual aspects of protein synthesis in mammalian systems, e.g., N-terminal modification of immunoglobulins and/or albumin, as well as the biosynthesis of the tripeptide thyrotropin releasing factor.

PULMONARY BRANCH—Michael A. Beaven, Ph.D.

The SECTION ON MOLECULAR PHARMACOLOGY has a broad interest in local tissue hormones, the biogenic amines (histamine, serotonin, and the catecholamines), the polyamines (putrescine, spermine, and spermidine), the prostaglandins, and the enzymes involved in the synthesis and degradation of these substances. The work is concerned with the role of these compounds in health and disease. Investigations have included: (1) the study of polyamines in tissues with rapid cell turnover, e.g., thymus lymphocytes, regenerating liver, and various tumors; (2) the release and synthesis of histamine, serotonin, and other tissue factors in inflammatory and allergic reactions in *in vivo* and *in vitro* systems; and (3) the effect of anti-imflammatory drugs in cell growth, metabolic activity in various mammalian cell culture systems. Current studies are directed toward the role of biogenic amines in lung and include investigations of the influence of age, infection, and allergic conditions on the synthesis and turnover of histamine and serotonin in lung. Normal and germ-free animals are being used for these studies. The work requires the use of sensitive isotopic assay procedures and particular emphasis is given to the possible use of these procedures in the diagnosis of disease.

PULMONARY BRANCH—Colin F. Chignell, Ph.D.

The SECTION ON MOLECULAR PHARMACOLOGY is concerned with the mechanism of drug action at the molecular level. Drug interactions with biological systems are being studied with a variety of physical and spectroscopic techniques including ultraviolet and visible absorption spectroscopy, fluorescence spectroscopy, nuclear magnetic resonance and electron spin resonance (including the use of spin labels), and optical rotatory dispersion and circular dichroism. Current areas of active research include the binding of drugs to plasma proteins, nucleic acids, membranes, and other cellular components, the binding of colchicine and its analogs to microtubule protein, the interaction of decamethonium and hexamethonium with acetylcholinesterase and acetylcholine receptor protein from *Torpedo californica*, and the inhibition of mammalian erythrocyte carbonic anhydrase by aromatic sulfonamides. Other projects are concerned with the mechanism of drug-induced phototoxicity and photoallergy and the characterization of lung surfactant lipoprotein.

LABORATORY OF CELLULAR METABOLISM—Martha Vaughan, M.D.

Major areas of research interest are (1) the mechanisms underlying hormonal control of lipolysis in fat cells, with emphasis at present on characterization of the hormone-sensitive lipase and elucidation of manner in which insulin, prostaglandins, and adrenal steroids affect the formation, degradation, and action of cyclic AMP, and (2) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides (e.g., prostaglandins, adrenal steroids) in regulation of growth and morphology of mammalian cells grown in culture, and (3) the nature and regulation of guanylate cyclases in smooth muscle and other cells.

National Institute of Allergy and Infectious Diseases

LABORATORY OF PARASITIC DISEASES—Eugene Weinbach, Ph.D.

The effects of drugs and other toxic agents on the metabolism of mitochondria are studied to provide a biochemical basis for their pharmacological activity. Current studies are concerned with electron transport, oxidative phosphorylation, ion translocation, and structure-function relationships in mitochondria. Particular attention has been given to compounds that uncouple oxidative phosphorylation and to their mechanism of action. A hypothesis concerning the mechanism of uncoupling of oxidative phosphorylation based on conformational changes in proteins involved in energy conservation has been derived from these studies. The work will be extended to determine if other pharmacologically active agents induce conformational changes in proteins and thereby alter their catalytic function.

National Institute of Child Health and Human Development

LABORATORY OF BIOMEDICAL SCIENCES—David C. Klein, Ph.D.

Investigations within the SECTION ON PHYSIOLOGICAL CONTROLS have focused on describing the molecular mechanisms through which hormones and biogenic amines regulate gene expression. The role of cyclic AMP in the regulation of the activity of enzymes and the regulation of indole metabolism has been one of the major areas of interest. Current research is concerned with the relationship between biogenic amines and the production and release of peptide hormones from neuroendocrine tissue. In addition, enzyme induction is being studied using biochemical and electrophysiological tools to understand the relationship between the biochemical and electrophysiological effects of neurotransmitters.

BEHAVIORAL BIOLOGY BRANCH—Phillip G. Nelson, M.D., Ph.D.

The BEHAVIORAL BIOLOGY BRANCH conducts research in neurobiology using tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations.

The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress.

DEVELOPMENTAL PHARMACOLOGY BRANCH—Daniel W. Nebert, M.D.

This branch investigates the molecular mechanisms underlying genetic differences and environmental factors influencing drug metabolism in man. The program includes a search to understand congenital malformations, the toxic or mutagenic or carcinogenic effect of drugs, the development of drug-metabolizing enzymes and their capacity to be induced or repressed, and jaundice caused by breast milk feeding. Genetics in mice and cell culture techniques are commonly used as experimental model systems. Attempts are being made to distinguish genetic factors from environmental influences and to develop methods for assessing or predicting a compound's teratogenic, toxic, mutagenic, or carcinogenic effect in man. This research complements and supports the on-going Institute programs in the Pregnancy Research Branch and the Neonatal and Pediatric Medicine Branch. Intent is to form an overall Perinatal Biology Program which will span the health concerns of children and mothers during both the prenatal and postnatal periods.

National Institute of Environmental Health Sciences

LABORATORY OF PHARMACOLOGY—James R. Fouts, Ph.D.

Research Programs: Pulmonary Group—use of isolated perfused lung in study of chemical uptake and effect of chemicals on nonrespiratory functions, lung physiology, and biochemistry. Collaboration with clinical groups at Duke University on chemical-induced lung disease. *Pharmacokinetics*—whole animal and isolated organ studies of rates and mechanisms of chemical uptake, storage, and release. Collaboration with GEIG, DRS groups in Bethesda. *Marine Pharmacology*—studies of mechanisms of pollutant accumulation in edible marine species; use of marine systems to detect waterborne pollutants. Field labs in Maine and Florida; interagency collaborative efforts, collaboration with university scientists here at NIEHS as well as in Maine and Florida. *Toxication-Detoxication*—toxication-detoxication systems in hepatic versus extra-hepatic tissues, species differences, developmental patterns; role of metabolic activation of chemicals in mutagenesis, teratology.

LABORATORY OF ENVIRONMENTAL TOXICOLOGY—Robert L. Dixon, Ph.D.

Scientific effort are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on the following tasks: (1) Determine mechanisms of teratogenesis using *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; (2) maintain an international teratology information center (ITIC); (3) assess environmental agents for their teratogenic potential; (4) study the molecular mechanisms underlying cellular differentiation; (5) evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; (6) understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; (7) determine the possible gestational origin of subtle toxic effects which do not become apparent until later in life; (8) define the effect of environmental agents on oogenesis and spermatogenesis; (9) examine the behavioral and neurological consequences of exposure to environmental substances; (10) develop preclinical predictors of toxicity using *in vitro* cells and tissues, lower animals, and biochemical test systems; (11) conduct studies focused at specific target organs to detect early or relatively low levels of toxicity and extrapolate these laboratory data to man.

National Institute of Neurological and Communicative Disorders and Stroke

LABORATORY OF NEUROPHYSIOLOGY—Jeffery L. Barker, M.D. and Thomas G. Smith, Jr., M.D.

The principal aims of the laboratory are to understand how nerve cells communicate and how CNS-active drugs alter neuronal communication. The preparations used include the mammalian CNS grown in tissue culture and amphibian and molluscan nervous systems studied *in vitro*. The methods used are primarily electrophysiological, including intracellular recording, voltage-clamp techniques and extracellular microiontophoresis. Specific projects include (1) comparison of neurotramsitter and peptide neurohormone functions at the single cell and defined circuit level, (2) the cellular pharmacology of general anesthetics, convulsants and anti-convulsants, and (3) biochemical analysis of rapidly transported proteins.

EXPERIMENTAL THERAPEUTICS BRANCH—Donald B. Calne, M.D.

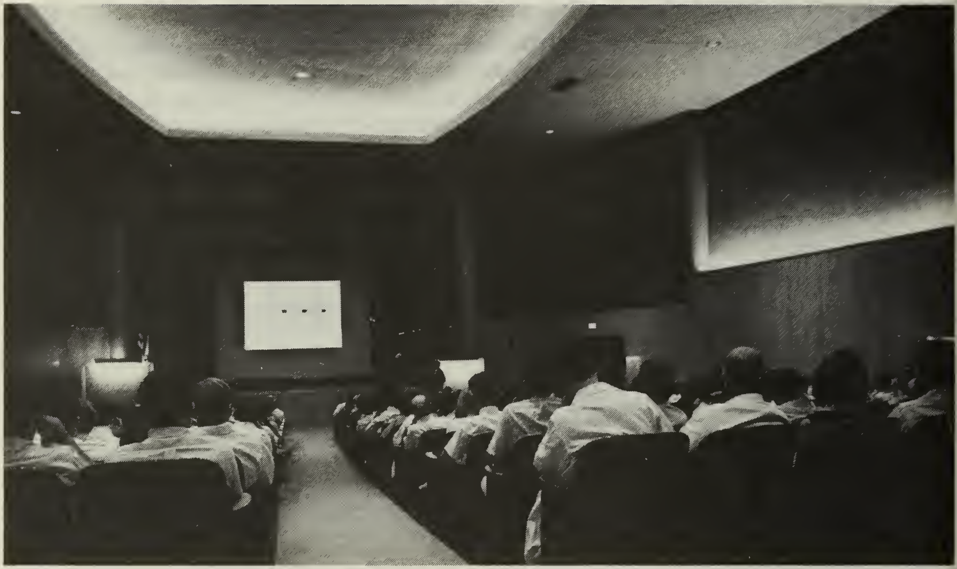
This branch conducts studies in three areas: (1) Drugs are investigated as potential therapeutic agents in patients with motor disorders in which central neuropathology has lead to identifiable changes in transmitter function and as tools to analyze the pharmacological disturbances accompanying neurological disorders. Animal models of neurological disease of the motor pathways are investigated to determine new ways of ameliorating neurological deficits and overcoming adverse reactions.

(2) Patients with severe seizure disorders are evaluated by new techniques including the study of efficacy and metabolism of such drugs as sodium valproate, methsuccimide, phensuccimide, and mephenytoin. Some projects are related primarily to clinical efficacy, but others, using techniques such as immunoassay, gas-liquid chromatography, and mass spectroscopy, involve pharmacokinetic studies as well as investigation of new metabolites of antiepileptic drugs.

(3) Receptors for neurotransmitters which are linked to adenyl cyclase are studied biochemically. Both the dopamine receptor in the caudate nucleus and the beta-adrenergic receptor in the cerebellum are utilized as model systems. The biochemical mechanism of action of drugs or endogenous compounds from the brain are evaluated in these systems. In addition, the levels of both catecholamine metabolites and drugs are quantitated with sensitive microassays; these measurements permit the evaluation of neurotransmitter function *in vivo*.

The Pharmacology Research Associate Committee

Choice of program area depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. The Pharmacology Research Associate Committee offers counseling to applicants invited to the NIH for interviews.



National Institute of Mental Health

John C. Eberhart, Ph.D., Director of Intramural Research
Robert A. Cohen, M.D., Ph.D., Director, Division of Clinical and Behavioral Research

This Institute offers an opportunity for postdoctoral research training in psychiatry and in the biological and behavioral sciences. Clinical Associates are assigned clinical responsibility in caring for patients who are admitted for both therapeutic and research purposes. Research Associates engage in laboratory research in one of the biological or behavioral science laboratories under the preceptorship of one of the senior staff, and may in addition participate in tutorial seminars and other teaching programs, as their needs and desire indicate.

The Clinical Associate Program is designed as a post-residency experience for psychiatrists with three years of training. Nevertheless, well qualified psychiatrists, with two years of residency, and physicians with other specialties, may be appointed. The Clinical Center is approved for a third year of psychiatric residency training.

Applications for the Clinical Associate Program are being accepted only for July 1979 appointments.

Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all associates to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Descriptions of the NIMH program areas to which associates will be appointed follow:

The BIOLOGICAL PSYCHIATRY BRANCH (William E. Bunney, Jr., M.D., Chief; Senior Staff: R. M. Post, M.D., J. C. Gillin, M.D., R. J. Wyatt, M.D., D. P. van Kammen, M.D., G. L. Brown, M.D., E. Gershon, M.D., M. Buchsbaum, M.D., L. Cytryn, M.D., D. McKnew, M.D., J. Rapoport, M.D., J. Tallman, Ph.D., C. Pert, Ph.D., A. Pert, Ph.D., M. Kafka, Ph.D.) conducts a broad program of research, training, and treatment of clinical psychiatric problems including schizophrenia, manic-depressive illness, drug abuse, and childhood mental illness. The focus of the Branch is psychobiological and brings together information from four disciplines—psychiatry, genetics, pharmacology, and biochemistry. Other research groups are concerned with psychogenetics, biochemistry of neurotransmission, twins and siblings, investigations of perception and cognition, and studies of the physiology of sleep and sleep changes in psychiatric illness. A general goal of the lab is to develop programs to investigate biological contributions to schizophrenia, manic-depressive illness and childhood mental illness.

Clinical Associates are assigned to one of six sections or units within the BIOLOGICAL PSYCHIATRY BRANCH.

The SECTION ON NEUROPSYCHOPHARMACOLOGY (D. P. van Kammen, M.D., Unit Chief). This 12-bed psychiatric research unit is involved in clinical and laboratory research of acute and chronic schizophrenia. The Clinical Associate will participate in and conduct studies concerning the pharmacological, genetic, biochemical, phenomenological and dynamic investigations of schizophrenia. Major current areas of interest involve: (1) the study of the role of dopamine in schizophrenia and the use of drugs with specific actions on dopamine metabolism. Metabolites of neurotransmitters and enzymes are being assessed in the urine, plasma and cerebrospinal fluid; (2) a multi-disciplinary approach to schizophrenia, in collaboration with other investigators of NIMH and other institutes; (3) attempts to delineate vulnerability markers (state-independent and state-related variables);

(4) prediction of antipsychotic drug response and prognosis; (5) exploration of GABA and neurotransmitter systems other than dopamine for their potential involvement in psychosis; (6) clinical assessment of pharmacological and endocrinological effects of the above-mentioned.

The SECTION ON PSYCHOGENETICS (E. Gershon, M.D., Unit Chief). The research goals of the Section are: (1) to identify familially transmitted biological and behavioral characteristics associated with the affective and other major psychiatric disorders, including pharmacogenetic and chromosomal-linkage investigation; (2) to identify the mode of genetic transmission; (3) to separate out familial and non-familial factors in the liability to the disorders; (4) to study in animal models the physiological role and nature of inheritance; (5) to develop mathematical models of inheritance appropriate to psychiatric disorders. The patients and relatives' studies are drawn from the present and past inpatients in the intramural program. The Section has a follow-up outpatient clinic for its studies.

The SECTION ON PSYCHOBIOLOGY (R. M. Post, M.D., Unit Chief). This 12-bed psychiatric research unit focuses on clinical and biological assessment and treatment of patients with manic-depressive illness, but also includes some patients with schizoaffective and schizophrenic illness. The interactions of psychological and biological parameters are studied, and mood, cognitive and behavioral variables are viewed in relation to such biological correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study of central amine metabolism in psychiatric patients utilizing various cerebrospinal fluid strategies—measurement of amine metabolites, electrolytes, cyclic nucleotides, and neuroendocrine parameters. Time course of biological effects of psychotropic drugs is studied in relation to clinical efficacy. New pharmacological agents are currently being tested including dopamine and norepinephrine receptor-stimulating drugs. The mechanisms underlying the paradoxical antidepressant effect of one night's sleep deprivation are being studied. Clinical and laboratory studies of psychomotor stimulants are ongoing. An active behavioral-pharmacology laboratory is maintained for the intensive study of the long term effects of psychomotor stimulant administration in rodents and primates as models for the development of psychosis.

The UNIT ON SLEEP STUDIES (J. C. Gillin, M.D., R. J. Wyatt, M.D.) is involved in studying the sleep patterns of the patients on the clinical research units. In addition to phenomena associated with various disorders, emphasis is placed on the biochemical substrates of sleep processes and their response to various pharmacological alterations.

The UNIT ON CHILDHOOD MENTAL ILLNESS (G. L. Brown, M.D., L. Cytryn, M.D., D. McKnew, M.D., J. Rapoport, M.D.) is a six-bed day and/or overnight hospitalization inpatient program operating jointly with the Section on Experimental Therapeutics, Laboratory of Clinical Science, currently focusing on hyperactivity and Gilles de la Tourette syndrome. Childhood psychoses and certain metabolic disorders of childhood are sometimes studied. Current focus is on (1) diagnostic assessment, treatment, and disposition; (2) pharmacokinetic studies of drugs given to children for clinical disorders; (3) studies of new drugs; (4) studies of kinetics and metabolism of neurotransmitter systems via body fluids; (5) studies of hormonal-neurotransmitter interactions; (6) genetic studies; (7) sleep studies, and (8) all of the foregoing in relationship to psychological and biological development (i.e., brain maturation). An outpatient program is also underway involving enuretic children, evaluation of children whose parents have been hospitalized here in the past for affective illness, and the follow up of formerly hospitalized children.

The UNIT ON STUDIES OF DRUG ABUSE is a program of inpatient evaluation on the research units of the clinical service. The drug abuse unit is currently focusing on

(1) problems of amphetamine as it represents a model psychosis for schizophrenia; (2) the phenomenology, biochemistry and pharmacology of the experience of "high" in man; and (3) central neurotransmitter metabolism.

The LABORATORY OF CLINICAL SCIENCE (Irwin J. Kopin, M.D., Chief; Senior staff: Julius Axelrod, Ph.D., M. H. Ebert, M.D., D. M. Jacobowitz, Ph.D., M. J. Brownstein, M.D., J. Saavedra, M.D., S. P. Markey, Ph.D., N. B. Thoa, Ph.D., R. W. Colburn, Ph.D.) conducts a program of research in biochemistry, pharmacology, physiology, medicine and psychiatry and the interrelationships between them. Applicants for the Research Associate program should have at least one year of clinical training while Clinical Associates are required to have had at least two years of post doctoral training in neurology or psychiatry before arrival for duty. Parts of the program have been accredited for one year of training in neurology, medicine, or psychiatry.

Current research includes: (1) studies in animals on the mechanism of action and metabolism of drugs and hormones which act in the central nervous system; (2) studies of the distribution and role of peptides and amino acid putative neurotransmitters in brain and spinal cord; (3) neuroendocrine control mechanisms and the role of specific putative neurotransmitters in animals and patients; (4) receptor systems for neurotransmitters and their modification by drugs, hormones, and activity in animals and patients; (5) synthesis, storage, release, actions, and termination of action of neurotransmitters and the effects of drugs, hormones, stress, biological activity and genetic and environmental factors on these processes; (6) determinants of plasma catecholamines and dopamine-β-hydroxylase for evaluation of sympathetic neuronal function in man and experimental animals in various disease states, drug treatment, stress, and endocrine status; (7) clinical pharmacology of drugs with important central nervous system actions, particularly drugs of importance in psychiatry and neurology; (8) application of mass spectrometry to use in metabolic studies using heavy isotopes to study amine metabolism in cerebrospinal fluid and blood; (9) determination of levels of various drugs in blood and CSF and correlating these with clinical response and changes in amine metabolites in CSF, blood or urine; (10) application of the techniques described above to studies in patients with disorders of metabolism relevant to psychiatry (such as disorders of amino acids metabolism), psychosomatic disorders, and some neuropsychiatric disorders (such as tardive dyskinesia). Clinical and biological studies of certain psychiatric disorders of childhood are being effected (e.g., the hyperactive and Gilles de la Tourette syndromes); and (11) psychological studies relating memory, especially state-dependent memory and learning, to effects of drugs and changes in clinical state. Thus, there is a well-rounded basic and clinical approach to research on a wide variety of biological aspects of neuropsychiatric function and disease. Furthermore, there is offered opportunity for interaction and collaborative research with other programs or investigators at the NIMH or other institutes of NIH.

The CLINICAL NEUROPHARMACOLOGY BRANCH (Dennis L. Murphy, M.D., Chief; Senior staff: Jonathan Costa, M.D., Ph.D.; Stanley Slater, M.D.) conducts a program designed to contribute to the understanding of the mechanisms of therapeutic drug effects in individuals with mania, depression, and other behavioral disorders. The studies are conducted on a 12-bed psychiatric research ward, with the support of a behavioral assessment and data processing program and a biochemistry laboratory under the direction of Dr. Costa. Clinical associates ordinarily enter the research group after 2 or 3 years of psychiatric residency training. Depending on prior research and clinical experience, they initially will participate in ongoing research projects and clinical care. With increased experience, they will ordinarily work with a senior staff member in the planning, design and implementation of one or more research projects to be conducted in the second year. Opportunities for specialized, in-depth study of the features and treatment of affective disorder subgroups are available. Emphasis is on the strategies and methods used in clinical research. Specific research projects range from psychological studies of the characteristics of individuals who do or do not respond to specific drugs to laboratory studies of the effects of drugs on cellular enzyme activity and transport processes. Drugs currently under study include natural precursors of brain neurotransmitters, lithium carbonate, d- and 1-amphetamine, MAO-inhibiting drugs, as well as some other new investigational compounds. Special areas of study at the present include: (1) studies of memory, especially state-dependent memory and learning, as affected by drugs and changes in clinical state; (2) drug response differences, neuroendocrine responses and other characteristics differentiating bipolar and unipolar depressed patients; (3) methods for behavioral and psychological state assessment; (4) studies of platelet and plasma amine oxidases; (5) amine storage, transport and cyclic AMP alterations; and (6) the serotonergic neurotransmitter system and behavior.

The CLINICAL PSYCHOBIOLOGY BRANCH (Frederick K. Goodwin, M.D., Chief) conducts clinical research in areas related primarily to affective illness (depression and mania) and its treatment, and laboratory research on the neurobiology of brain proteins, peptides and neurotransmitter amines. Structurally the Branch is divided into the Clinical Research Unit, the Unit on Neurochemistry and the Outpatient and Follow-Up Unit. Throughout the 2- to 3-year assignment the Associates' time is divided among clinical care-ward management, clinical research and laboratory research, depending on interests. Direct responsibility for research projects is assumed in the beginning.

The CLINICAL RESEARCH UNIT (Thomas Wehr, M.D., Chief) represents the major research resource of the Branch and is located on a 15-bed psychiatric research ward. Ongoing clinical projects include the following: (1) Under the direction of Dr. Philip Gold, the development of neuroendocrine strategies for the evaluation of hypothalamic-pituitary function and the integration of these measures with the study of amine metabolites from spinal fluid and urine. A wide range of consultation and collaboration with endocrine groups in other Institutes is afforded by Dr. Gold's full participation in the Inter-Institute Endocrine Program; (2) studies of biological rhythms, under the direction of Dr. Wehr, involve exploration of both diurnal rhythms and longer term cycles; amine and melatonin rhythms are of special interest; (3) the evaluation of state-dependent versus state-independent variables in behavioral-biological correlations; (4) the differential biochemical response to stress in depression-prone individuals compared to normals; (5) the differential biochemical mechanisms of the acute versus the prophylactic actions of lithium in manic-depressive patients; (6) the efficacy of hormonal potentiation of antidepressant drugs; (7) the biochemical identification of patient subgroups which predict drug response; (8) the interrelationship between drug action and psychodynamics of manic and depressive patients, and others.

The UNIT ON NEUROCHEMISTRY (Paul Marangos, Ph.D., Chief) develops and maintains methods for the assessment of urinary and spinal fluid amine metabolites, in addition, immunoassays for hypothalamic peptides are under development. Animal studies are focused on the characterization, localization, and functional definition of Neuron Specific Protein (NSP) and mechanisms of psychotropic drugs are explored, particularly in relation to brain proteins, peptides and neuronal receptor function. Primates are used in studies of biological rhythms and the effects of drugs.

The OUTPATIENT AND FOLLOW-UP UNIT (Philip Gold, M.D., Chief) operates a clinic for the maintenance treatment and long-term evaluation of recurrent affective disorder. Studies of the "well state" are integrated into prophylactic drug trials; the influence of psychosocial and pharmacological factors on outcome is an area of special interest. A complete list of current research projects is available on request.

The LABORATORY OF NEUROBIOLOGY (Ichiji Tasaki, M.D., Chief; Senior staff: Robert H. Wurtz, Ph.D.) conducts research on the nervous system at several levels ranging from biochemical and biophysical studies of single excitable cells to studies of systems of neurons in the brain. Current research projects include studies on: (1) The excitation process in nerve and muscle membrane using recently developed optical techniques to demonstrate changes in birefringence, absorbance, and fluorescence in excitable tissue during an action potential; (2) biophysics of model membrane systems; and (3) the integration in the brain of visual information and extravisual input (such as eye movements and attention) using single unit recording in awake monkeys performing a learned task.

The LABORATORY OF GENERAL AND COMPARATIVE BIOCHEMISTRY (Giulio L. Cantoni, M.D., Chief; Senior staff: Werner A. Klee, Ph.D., Carl R. Merril, M.D., Stuart H. Mudd, M.D.) conducts investigations on mechanisms and pathways of protein biosynthesis; biological methylations; alkaloid biosynthesis; differentiation and gene expression in eukaryotes.

The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, RNAse action, mechanism of drug addiction, muscle differentiation in cell culture, and transgenosis.

The SECTION ON ALKALOID BIOSYNTHESIS studies the enzymes involved in alkaloid biosynthesis, their control and biosynthesis in relation to morphogenetic development of the plant; also, enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

The LABORATORY OF CEREBRAL METABOLISM (Louis Sokoloff, M.D., Chief; Senior staff: Marian W. Kies, Ph.D., Russell E. Martenson, Ph.D., Elaine E. Kaufman, Ph.D., and Charles Kennedy, M.D.) The SECTION ON DEVELOPMENTAL NEUROCHEMISTRY conducts a broad program of investigations on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the central nervous system. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones, which play important physiological roles in CNS function. Present emphasis is on the mechanism of action of thyroid hormones, not only on the maturation of the nervous system, but also on metabolic processes in all susceptible tissues. A method has recently been developed in this laboratory which permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiological and pathological states.

The LABORATORY OF NEUROCHEMISTRY (Seymour Kaufman, Ph.D., Chief; Senior staff: Howard A. Nash, M.D., David M. Neville, Jr., M.D., and Audrey L. Stone, Ph.D.) conducts investigations in the following areas: (1) the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine hydroxylating system. In addition to studies with the pure enzymes, there is emphasis on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia; (2) the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin and the relationship between the properties of the enzymes and physiological regulation of rates of synthesis of these neurotransmitters; (3) the biochemical basis for skeletal muscle hypertrophy including the effects of exercise and neural factors in the process; (4) cell surface membrane proteins and receptors in their role in cellular differentiation; and (5) the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

The LABORATORY OF NEUROPHYSIOLOGY (E. V. Evarts, M.D., Chief; Senior staff: Frederick A. Miles, Ph.D. and Stanley I. Rapoport, M.D.) conducts research on (1) neural control of movement; (2) plasticity of stimulus-response relations; (3) the physiology and pharmacology of the blood-brain barrier; and (4) metabolic correlates of brain activity.

The studies on neural control of movement are designed to elucidate the functional interrelations between motor subsystems (e.g., spinal cord, brain stem, cerebellum, basal ganglia, thalamus, and cerebral cortex). This work involves behavioral, electrophysiological, and neuroanatomical techniques. Projects are aimed at understanding both reflex and voluntary motor function. Studies on control of eye movements focus both on the vestibulo-ocular reflex and on saccadic movements. Discharges of single nerve cells are recorded with microelectrodes in monkeys trained to carry out movements, and the results are interpreted in relation to the anatomical input-output properties of the loci from which recordings are obtained.

Work in the area of plasticity of stimulus-response relations involves: the role of segmental and suprasegmental neural factors in determining the modifications of muscular activity associated with motor learning in man and subhuman primates. Studies also focus on mechanisms underlying adaptive changes in the vestibulo-ocular reflex in the monkey.

The blood-brain barrier, which regulates cerebral metabolism and function, is opened reversibly for experimental pharmacology, its structure at cerebral blood vessels is elucidated with electron microscopy, and the principles regulating transport are determined by experimental and theoretical means.

Increased neuronal activity is associated with increased neuronal metabolism, and techniques for detecting localized changes in cerebral metabolism are now being used to discover the location and magnitude of metabolic changes associated with a variety of different cerebral functional states. Studies are currently focused on discovering cerebral metabolic processes underlying sleep and motor behavior.

The LABORATORY OF BRAIN EVOLUTION AND BEHAVIOR (Paul D. MacLean, M.D., Chief; Senior staff: John B. Calhoun, Ph.D., and Walter C. Stanley, Ph.D.) offers opportunities for research on evolutionary, developmental, and ecological factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals living under semi-natural conditions. The laboratories are equipped for neuroanatomical research, microelectrode recording, brain stimulation, psychological testing, and a computer system with high speed graphics capability for recording and processing electrophysiological and behavioral data. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior. Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, and ecology. The laboratory is beautifully located at the NIH Animal Center near Poolesville, Maryland, with open fields, a large pond for water fowl, and woodlands.

The Division of Special Mental Health Research (R. J. Wyatt, M.D., Acting Director) located at Saint Elizabeths Hospital, (1) plans and conducts a program of intramural research on special mental health problems such as psychopharmacology, neuropharmacology, memory, and human behavior and (2) performs clinical evaluation and followup activities in connection with research patients.

The Laboratory of Clinical Psychopharmacology (Richard J. Wyatt, M.D., Chief; Senior staff: J. Christian Gillin, M.D., Thomas Reynolds, M.D., Llewellyn Bigelow, M.D., Farouk Karoum, Ph.D., David Stoff, Ph.D., Wallace Mendelson, M.D.) conducts a multidisciplinary research program utilizing pharmacologic, biochemical, physiological, and psychological techniques to study normal and abnormal behavior. The main research areas at the present time are (1) schizophrenia, with particular interest in postulated underlying biochemical mechanisms and abnormalities. Our current research interests include (a) the significance of our finding that schizophrenic patients exhibit a genetically determined low level of platelet monoamine oxidase activity, (b) hypothesized abnormalities of serotonin and dopamine in schizophrenia, (c) the role of postulated endogenous psychotogens such as dimethyltryptamine (DMT) in psychotic illness, (d) new experimental pharmacologic treatments of schizophrenia, and (e) mathematical models for the behavior of hospitalized schizophrenic patients; (2) sleep, including sleep abnormalities in psychiatric illness, biochemical and endocrine factors during sleep (in health and disease) and specific sleep disorders such as narcolepsy (some of these studies are done at the Clinical Center); (3) mind-altering drugs, such as the role of marijuana in the state-dependent learning and perception, animal behavioral models of psychotogens, and the psychological and biochemical effects of postulated endogenous psychotogens in normal volunteers; (4) presenile dementia, including biochemical, pharmacologic, and sleep studies; (5) biochemical and pharmacological techniques, including use of the gas chromatograph and mass spectrometer, to assess functioning of the central nervous system. The Laboratory operates three research wards of 12 beds each for studies on psychiatric patients and normal volunteers. In addition, it is equipped with biochemical and human psychophysiologic laboratories, computer facilities, and animal space for behavioral psychopharmacology, sleep studies, and biochemistry. Associates are encouraged to be at the interface between the laboratory and the clinic and we make every effort to ensure the development of competence in both areas.

The Laboratory of Neuropharmacology (Richard J. Wyatt, M.D., Acting Chief; Senior staff: F. F. Weight, M.D.) conducts a multidisciplinary research program centered upon the identification of synaptic transmitter substances, and the mechanisms by which neuro-active and psycho-active drugs exhibit effects upon synaptic transmission. The approach is entirely at the cellular level, utilizing intracellular and extracellular electrophysiologic techniques, micromethods of drug administration including microelectrophoresis, and cytochemical studies with light, fluorescence, and electron microscopy. Specifically, studies are currently being carried out on: (1) the characterization and pharmacology of potential monoamine-containing neuronal pathways in the mammalian central nervous system; (2) the relation between pharmacological responsiveness and development of structurally specialized synapses; (3) the cytologic and physiologic organization of sympathetic ganglia.

The LABORATORY OF PRECLINICAL PHARMACOLOGY (E. Costa, M.D., Chief). The scientific efforts of the laboratory are directed to elucidating neuronal control mechanisms which mediate responses of drugs affecting neuronal function. The laboratory is organized into one group and four sections:

GROUP ON HIGH PRESSURE LIQUID CHROMATOGRAPHY (J. Meek, Ph.D.) develops new methods to investigate drug effects on renovation rates of brain stores of monoamines and neuropeptides.

SECTION ON MOLECULAR PHARMACODYNAMICS (D. L. Cheney, Ph.D., Acting Chief; Senior staff: C. C. Mao, Ph.D.) conducts pharmacological studies on (1) the dynamics of acetylcholine in discrete brain nuclei using pulses of deuterated precursors and mass fragmentography; (2) the dynamics of γ-aminobutyric acid in discrete brain nuclei using pulse labelling with ^{13}C glucose and mass fragmentography; (3) the regulation of the dynamics of acetylcholine and γ-aminobutyric acid by various endogenous neuropeptides.

SECTION ON BIOCHEMICAL PHARMACOLOGY (N. H. Neff, Ph.D, Chief) conducts investigations directed at: (1) identifying control mechanisms for enzymes which regulate the dynamics of putative brain neurotransmitters and (2) determining drug actions on the regulation of turnover rate of brain monoamines using mass fragmentography.

SECTION ON NEUROENDOCRINOLOGY (A. Guidotti, M.D., Chief) conducts studies concerning (1) the molecular mechanisms involved in the transsynaptic induction of tyrosine hydoxylase; (2) the activation of cAMP-dependent protein kinases in relation to the neuroendocrine control of pituitary and pineal glands.

SECTION ON MOLECULAR NEUROBIOLOGY (E. Costa, M.D., Chief; Senior staff: Y. T. Yang, Ph.D., D. M. Chuang, Ph.D., and J. Schwartz, Ph.D.) conducts studies on (1) the regulation of nerve growth factor production by glial cells; (2) the role of chromatine phosphorylation in the regulation of gene expression; (3) pharmacology of binding of putative neurotransmitters to postsynaptic receptors; (4) the regulation of storage, release and synthesis of peptides that function as putative neurotransmitters (enkephalines, substance P, angiotensin, neurotensin, etc.) and (5) the identity and kinetic properties of enzymes which regulate synthesis and metabolism of neuropeptides.

National Institute of Neurological and Communicative Disorders and Stroke

Donald B. Tower, M.D., Ph.D., Director
Richard L. Irwin, Ph.D., Laboratory Director

GENERAL. The National Institute of Neurological and Communicative Disorders and Stroke conducts, fosters, and coordinates research on the causes, prevention, diagnosis, and treatment of neurological and sensory disorders and related fields, and administers a program of research and training grants and awards.

Throughout the Institute, opportunities also exist for clinical and professional education, including many scientific disciplines.

Intramural Research Program

Thomas N. Chase, M.D., Director
Donald B. Calne, M.D., Clinical Director

The MEDICAL NEUROLOGY BRANCH (W. King Engel, M.D., Chief) has as its major function the application of basic research techniques to the investigation of clinical neurological problems. The Clinical Associate becomes acquainted with a majority of the neurological diseases with particular emphasis on the disorders of muscle, myasthenia gravis, lower motor neuron diseases, metabolic abnormalities of the central nervous system, and genetically determined disorders. He receives instruction in clinical neurology and the related clinical and basic sciences while developing an understanding of the various laboratory techniques which support the neurological investigation. During the first 12 months he is in a ward environment and is responsible for the care of patients on the Medical Neurology Service and the integration of related research. He covers the neurologic consultations to the other clinical services during 3 of those months. During the first year he is expected to learn to perform one of a variety of basic laboratory techniques (such as histochemistry, tissue culture, biochemistry, electon microscopy, immunology, autoradiography, or electromyography) as it applies to a clinical problem. The second year is spent in full-time work on that clinical research technique. Some Clinical Associates may stay a third year to continue their clinical research activities. The program is accredited for 1 year of residency training in neurology.

The SURGICAL NEUROLOGY BRANCH (Ayub K. Ommaya, M.D., F.R.C.S., Acting Chief) investigates problems in neural trauma, brain tumors, the surgical prophylaxis of strokes, and cerebrovascular disease management.

The Clinical Associate is required to study and has responsibility for the care of patients with brain tumors, strokes, and vascular malformations of the nervous system, and others with a variety of neurological disease. He receives practice and instruction in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating theater. He is also assigned to one of a number of laboratory projects designed to provide animal model correlation with the human disease under study. He is expected to learn and use new experimental techniques and work in collaboration with Senior Scientists.

The BRANCH OF CLINICAL NEUROSCIENCES (Cosimo Ajmone Marsan, M.D., Chief) consists of two sections: Clinical Neurophysiology and Functional Neurosurgery. The Branch involves a relatively small, highly specialized patient population in addition to that referred from the entire Clinical Center for EEG examination. The position of Clinical Associate in Neurosurgery is for a 2- or 3-year appointment. Preference is given to persons with basic neurological or neurosurgical training. Appointments in neurophysiology are also for 2 or 3 years. Preference is given to people with some previous experience in the field of electrophysiology and a knowledge of neuroanatomy. Current research: experimental epilepsy, involuntary movements, thalamo-cortical relationship, nature of brain waves, microelectrode study of cortical neurons, etc.

The DEVELOPMENTAL AND METABOLIC NEUROLOGY BRANCH (Roscoe O. Brady, M.D., Chief; Anatole S. Dekaban, M.D., Associate Chief for Clinical Investigation). The branch is devoted to cross-disciplinary basic investigations and clinical studies of disorders of the nervous system. The research deals with (1) the pathological biochemistry, diagnosis, and therapy of inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, and Tay-Sachs disease; (2) functional abnormalities of the nervous system, including epilepsy; (3) heritable and acquired demyelinating conditions such as multiple sclerosis; (4) the metabolism of complex lipids in tumorigenic virus-transformed cells; (5) the role of gangliosides in the interaction of glycoprotein hormones with cell membranes; and (6) molecular basis of nerve excitation as related to the structural and functional sidedness of natural and artificial membranes.

The Branch is comprised of the SECTION ON ENZYMOLOGY AND GENETICS (Dr. R. O. Brady, Head), The SECTION ON NEUROCHEMICAL METHODOLOGY (Dr. A. E. Gal, Head), the SECTION ON PHYSIOLOGY AND METABOLISM, (Dr. E. G. Trams, Head), and the SECTION ON CLINICAL INVESTIGATIONS AND THERAPEUTICS (Dr. A. S. Dekaban, Head). The first three sections are primarily devoted to basic research; in- and outpatient study is included in the SECTION ON CLINICAL INVESTIGATIONS AND THERAPEUTICS.

The EXPERIMENTAL THERAPEUTICS BRANCH (Donald B. Calne, M.D., Chief), conducts basic as well as clinically applied studies of central neurotransmitter mechanisms and their relation to the pathogenesis of various disorders of the nervous system. Current research projects include (1) studies of the synthesis, metabolism, release, and receptor interactions of monoamines, γ-amniobutyric acid and other central neurotransmitters; (2) mechanisms of action of drugs which affect the nervous system; (3) clinical and biochemical studies of patients with disorders such as parkinsonism, epilepsy, and chorea; and (4) clinical assessment of new therapeutic agents.

The Branch consists of the THERAPEUTICS SECTION (Dr. Donald B. Calne, Head), the PHARMACOLOGY SECTION (Dr. Thomas N. Chase, Head), the CLINICAL EPILEPSY SECTION (Dr. Kiffin Penry, Head), as well as units on physiological, behavioral, and biochemical neuropharmacology.

The INFECTIOUS DISEASES BRANCH (J. L. Sever, M.D., Ph.D., Chief), conducts studies of acute and chronic disease and infections of the central nervous system. Both clinical and laboratory investigations are pursued in the areas of (1) neurovirology; (2) immunochemistry and clinical investigations; (3) neurogenetics; (4) electron microscopy; and (5) experimental pathology. These studies utilize new techniques for virus recovery; cellular and humoral immune response tests; virus serology, human volunteer and clinical trials; genetic techniques and HLA-MLC tissue typing; electron microscopy as well as experimental studies with small animals and non-human primates. Current emphasis is on multiple sclerosis, Parkinson's disease, SSPE, ALS, Reye's syndrome, and perinatal infections which damage the developing fetus. New techniques are being developed to detect acute and chronic infections of the central nervous system. Training is provided in the five investigative areas listed above, and clinical experience with these investigations is available.

The NEUROIMMUNOLOGY BRANCH (Dale E. McFarlin, M.D., Chief) has recently been established. This group is doing research in the following areas: (1) Characterization of the immune response to viral agents; in particular, agents such as measles which cause chronic infection in patients with neurological diseases, and certain animal models are being studied; (2) assessment of the immune response to membrane components of membranes in the peripheral and central nervous system; (3) evaluation of immune function in patients with chronic neurological disorders of unknown etiology such as multiple sclerosis and parkinsonism which may be related to either an atypical infection of the nervous system or immunopathologic mechanisms; (4) projects involving the clinical assessment of new therapeutic agents are planned in the future.

LABORATORY OF NEURO-OTOLARYNGOLOGY (Jorgen Fex, M.D., Ph.D., Chief). This laboratory is a new facility. The mammalian inner ear is being studied, using techniques of anatomy, biochemistry, and neurophysiology. A project is underway to study inner ear mechanisms of synaptic excitation in the mammal. A second project concerns synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A major, long-term program of the laboratory is to solve problems concerning hereditary hearing disorders in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models.

LABORATORY OF NEUROCHEMISTRY (Janet V. Passonneau, Ph.D., Chief) conducts research into the molecular events that underlie the normal functioning of the nervous system and derangements which occur in neurological diseases. The Laboratory consists of three sections: the SECTION ON CELLULAR NEUROCHEMISTRY (J. V. Passonneau, Head), the SECTION ON ENZYME CHEMISTRY (R. W. Albers, Ph.D., Head), and the SECTION ON NEURONAL DEVELOPMENT AND REGENERATION (A. A. Zalewski, M.D., Acting Head). The current investigations of the Laboratory employ a variety of disciplinary approaches and methodologies and encompass studies on isolated enzymes, neuronal cells in culture, and neuronal metabolism in intact animals. Programs relate to the molecular mechanisms subserving the generation of membrane potentials, the structure of excitable membranes, neurotropic factors, neuronal regeneration, effects of ischemic and convulsive disorders, and cyclic nucleotide metabolism among others.

The LABORATORY OF MOLECULAR BIOLOGY (Ernst Freese, Ph.D., Chief) examines the molecular mechanisms of biological processes that are affected in hereditary and viral diseases or in teratogenic effects.

In the MOLECULAR VIROLOGY SECTION (R. A. Lazzarini, Ph.D., Head) the control of cellular and viral RNA synthesis is studied in tissue cultures. In particular, the transcription and replication of the myxo- and paramyxoviruses are examined at the molecular level.

In the SECTION ON DEVELOPMENTAL BIOLOGY (Ernst Freese, Ph.D., Head) the transport of substrates through cellular membranes and other membrane-associated phenomena are studied in growing and differentiating bacteria and tissue cultures, as well as in isolated membrane vesicles. The inhibition of these reactions by lipophilic compounds, present in the human environment and partly known to have neurological effects, is analyzed. In addition, the section determines the biochemical reason why compounds accumulating in cacogenic mutants prevent normal development or produce hereditary diseases, and it endeavors to find means of avoiding this accumulation or preventing its effect. Bacterial systems, with their powerful genetic and biochemical possibilities, are compared with human tissue cultures.

The LABORATORY OF NEUROPATHOLOGY AND NEUROANATOMICAL SCIENCES (Igor Klatzo, M.D., Chief) recognizes scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomical sciences. Thus investigations on basic pathogenic mechanisms operative in various neuropathological conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system. Specific problems under current investigation are: Cerebral ischemia, hypoxía, brain edema, role of the glia, development and pathology of myelin, control of carbohydrate metabolism, aspects of vascular permeability and transport mechanisms in the brain, mechanisms of neurohormonal regulation, localization of catecholamines, elucidation of some of the sensory and motor systems, investigation of neural membranes, junctional complexes, as well as the source and fate of synaptic vesicles. The main technical approaches include light and electron microscopy, freeze-fracturing, histochemistry, radioisotopic, biochemical and microchemical assays, and tissue culture. The laboratory is divided into six sections: (1) The SECTION ON FUNCTIONAL NEUROANATOMY (Thomas Reese, M.D., Head); (2) the SECTION ON NEUROCYTOLOGY (Milton Brightman, Ph.D., Head); (3) the SECTION ON EXPERIMENTAL NEUROPATHOLOGY, (Jan Cammermeyer, M.D., Head); (4) the SECTION ON CEREBRAL VASCULAR PATHOLOGY (Igor Klatzo, M.D., Head); (5) the SECTION ON CELLULAR NEUROPATHOLOGY (Henry Webster, M.D., Head); and (6) the SECTION ON NEUROCYTOBIOLOGY (Maria Spatz, M.D., Head).

The LABORATORY OF NEUROPHYSIOLOGY (M. G. F. Fuortes, M.D., Chief) conducts research on basic properties of nerve cells and on the organization of the nervous system. The morphology of cells, synapses and subcellular structures is studied by means of optical and electron microscopy. Membrane properties of receptor cells and central neurons are investigated by electrophysiological methods. Work on receptor functions include kinetic studies aimed at determining the properties of the transduction processes. The properties of central neurons and synapses are studied in simple preparations derived from vertebrates and invertebrates. Electrical and chemical properties of cells in tissue culture are also being investigated.

The LABORATORY OF EXPERIMENTAL NEUROLOGY (William F. Caveness, M.D., Chief) includes the following activities: (1) The investigation of the delayed effects of high energy radiation to the whole brain of the *Macaca mulatta* according to clinical therapeutic regimens. The functional alterations are monitored with clinical examinations, funduscopic photography, EMI scans, and chemical analyses of cerebrospinal fluid at four week intervals following exposure. At eight week intervals, the brains are subjected to definitive histological examination at a collaborating facility; and (2) the study of development and propagation of focal seizures in the developing brain of the monkey with the use of electrophysiological and regional blood flow, and regional glucose utilization techniques. Particular attention is directed to the subcortical nuclear masses.

One Research Associate position is available for 1 to 2 years. Previous experience in neuroanatomy or neuropharmacology is essential.

The LABORATORY OF NEURAL CONTROL (Robert E. Burke, M.D., Acting Chief) conducts fundamental research on the properties of mammalian nerve cells and on the organization of the mammalian central nervous system with particular reference to studies of the control of movement. Current experimental studies involve three main areas: (1) The central nervous system control of spinal cord motoneurons and the control exerted by these cells in turn on the muscle fibers innervated by them; (2) the organization of information processing systems in the spinal cord; and (3) the activity of central neurons and peripheral afferents during normal movement in intact animals. Such studies utilize both established and newly developed techniques for electrophysiological recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The Laboratory has facilities for development of specialized experimental equipment and novel electrode designs, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

The CENTRAL NERVOUS SYSTEM STUDIES LABORATORY (D. Carleton Gajdusek, M.D., Chief) is engaged in two studies: (1) Complete medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior and learning; and (2) slow, latent, and temperate virus infections of the central nervous system, with particular attention to chronic degenerative neurological disease and basic virological and immunological studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie and mink encephalopathy) which form a new group of microorganisms tentatively called ''viruses,'' although containing much smaller genetic information and possessing very different properties than any other group of viral agents. The biological and molecular characterization of these unconventional viruses is the major focus of the work. Aspects of learning and socialization in primitive disappearing cultures are documented using still and cinema photographic recording and sound recording. New methods of handling such data are developed.

Neurological Disorders Program

J. Kiffin Penry, M.D., Director

The goal of the Neurological Disorders Program is to plan and direct a program of grant and contract support for research and research training on neurological disorders to insure maximum utilization of available resources in attainment of Institute objectives; and to collaborate with intramural programs in the Institute and NIH-wide. The program is charged with the study of national priority diseases such as epilepsy, developmental disorders of children and adults, sclerosing and neuromuscular disorders, infectious diseases and tumors of the central nervous system, neuroendocrine studies, and learning, behavior and other sensory disorders. A number of the studies underway are collaborative studies which encompass the input of a number of outside institutions. The following programs are conducted by the Neurological Disorders Program of NINCDS.

The EPILEPSY BRANCH, under J. Kiffin Penry, M.D., develops and coordinates organized and directed research programs on a multi-institutional, geographic, or a multidisciplinary basis through its support of five comprehensive programs, each serving a specific geographical area. It develops, conducts, and coordinates collaborative and directed research programs aimed at finding new or improved methods of diagnosis, treatment, and prevention of convulsive disorders. The clinical investigation of new antiepileptic drugs is a major concern. The Branch fosters the synthesis, screening, and pharmacologic and metabolic investigation of antiepileptic drugs to collaborative efforts; also within its own facilities conducts research on the metabolism of anticonvulsant drugs and the treatment of certain difficult seizure disorders according to rigid protocols; fosters research in experimental models of epilepsy, and improved patient treatment through the use of serum antiepileptic drug determinations.

The DEVELOPMENTAL NEUROLOGY BRANCH, under Joseph S. Drage, M.D., plans and implements a program of grant and contract supported research on the neurological basis of developmental disorders of children, including the areas of cerebral palsy, autism, mental retardation, learning and behavioral disorders, central nervous system birth defects, heritable muscle and neurological diseases, and minimal brain dysfunction; assesses need for research and research training in such areas; determines and recommends program priorities and funding levels for such areas; consults with professional and voluntary health organizations in identifying, developing, and implementing a research program focused on the neurological basis of developmental disorders of children; provides for the archival and retrieval system of the Collaborative Perinatal Project data and promotes the appropriate use of this national data resource commensurate with the goals and mission of the NINCDS.

The Clinical Center

Mortimer B. Lipsett, M.D., Director
Griff T. Ross, M.D., Ph.D., Deputy Director
Philippe V. Cardon, M.D., Associate Director

The Clinical Center appoints Clinical Associates for the Departments of Diagnostic Radiology, Blood Bank, Clinical Pathology, and Nuclear Medicine. Associates in Diagnostic Radiology are expected to have completed their residencies prior to entrance on duty.

The BLOOD BANK DEPARTMENT (Paul V. Holland, M.D., Chief) is accepting applications for Clinical Associates under the matching system. Applicants with at least 1 year of training post internship are preferred.

The Department supplies over 20,000 blood products annually for transfusion to patients with unique hematologic and immunologic problems. The use of blood components is stressed, with increasing emphasis on the use of frozen red cells in appropriate clinical situations. The medical staff consists of four full-time staff physicians and one clinical associate, as well as residents and medical students who are present for varying periods of training.

In addition to its service function, a significant proportion of Blood Bank activity is oriented toward clinical and basic research. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various Institutes. Current programs include investigations into hepatitis and the hepatitis B (Australia) antigen, the effects of biologic incompatibilities on transfusion and transplantation, immunologic studies of drug-induced hemolytic anemias, and the use of computers in laboratory medicine.

The program offers training for the clinician in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. A close professional liaison is maintained with the Clinical Pathology Department through an active program of lectures, rounds, and seminars.

The CLINICAL PATHOLOGY DEPARTMENT (Ronald J. Elin, M.D., Ph.D., Chief) is accepting applications for Clinical Associates whose interests lie in specialized training and research in laboratory medicine. The department is organized into four main services: Clinical Chemistry, Hematology, Microbiology, and the Laboratory Computer Service. These areas are staffed by over 100 professional and technical personnel who form the operational base for the broad spectrum of laboratory diagnostic services called upon by the various Institutes for their intramural patient care programs. In addition, the professional staff of the department is engaged in collaborative and independent research in the areas relevant to laboratory medicine and the clinical diagnostic problems encountered at the Clinical Center. The department participates in the training of Residents in Clinical Pathology and interacts fully and on a professional consultative basis with the clinical programs at the National Institutes of Health.

Among the procedures and programs currently in operation in the department are automated assay systems for laboratory diagnosis, carbohydrate chromotography, amino acid analysis, gas chromatography, radioimmunoassays, mineral metabolism studies, coagulation factor studies, certain host-defense mechanisms in infectious diseases, properties of bacterial endotoxins, diagnostic anaerobic bacteriology, and new approaches in the interface between computer-assisted laboratory automation and data processing. These latter programs, in particular, are facilitated by direct access to the department's own computer facilities.

A close professional liaison is maintained with the Blood Bank Department.

A Clinical Associateship in any of the four services offers a broad experience in clinical and laboratory medicine. Each service carries on an active consultative role and participates extensively with many of the clinical services. In addition, each service provides supervised instruction in the functions of that area and opportunities are available for developmental investigation of the procedures of the clinical laboratory.

The DEPARTMENT OF DIAGNOSTIC RADIOLOGY (John L. Doppman, M.D., Chief).

Four Staff Radiologists are selected each year from among those applicants who have completed their residencies in Radiology or Diagnostic Roentgenology (Board certification not required). Such appointments are made for a period of 2 years with occasional opportunity for reappointment.

The department is well equipped to provide the routine and special diagnostic radiographic examinations needed by the 27,500 patients seen each year. The preselection of patients for admission to the NIH insures a challenging and stimulating gamut of diagnostic problems.

Thirteen radiologists comprise the professional staff and an adequate supporting staff is provided.

Facilities are available for both collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

The DEPARTMENT OF NUCLEAR MEDICINE (Gerald S. Johnston, M.D., Chief). One Clinical Associate is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in Nuclear Medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved Internal Medicine, Radiology, or Clinical Pathology is recommended in order to meet the requirements for certification by the American Board of Nuclear Medicine.

The American Medical Association has approved the department for a 2-year residency training program in Nuclear Medicine. Qualifications for trainees include at least 2 years of prior training in Radiology, Pathology, or Internal Medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital and the Maryland University Hospital.

The department consists of four sections: Diagnostic Nuclear Medicine Section, Whole Body Counter Section, Radiopharmacy Section, and Applied Physics Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various Institutes working within the Clinical Center. Dual probe rectilinear scanners and gamma cameras are the basic imaging devices. Dedicated computers supported by NIH computer experts from DCRT are located within the section. The Applied Physics Section and DCRT personnel work cooperatively in the development of new diagnostic techniques. The Whole Body Counter Section works closely with the Diagnostic Section and the Radiation Safety Office. It operates three whole body counters and provides a consultation service to all the Institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staffs of the Diagnostic and Whole Body Counter Sections consist of seven physicians, a radiobiologist, two physicists, an equipment specialist, six nuclear medical technicians, and three clerks. Departmental professionals are encouraged to interact with members of the various Institutes in order to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases.

The Radiopharmacy Section employs three full-time radiopharmacists, a technician, and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by Diagnostic Nuclear Medicine. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

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PART FOUR

Academic Programs Available to Associates

Among the academic programs open to an NIH Associate are: Evening courses provided by the Foundation for Advanced Education in the Sciences, Inc.; formal seminars under the direction of NIH staff; Combined Clinical Staff Conferences; formal lectures; symposia; and an annual scientific equipment exhibit. The ''NIH Calendar of Events'' lists 25 to 30 programs each week. Other events of interest are held at universities and other institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by The Graduate Program of the Foundation for the Advanced Education in the Sciences, Inc. Established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science, the Foundation is a non-Federal independent organization as defined by the Government Employees Training Act; however, its tuition and other fees can be paid by a Federal employer. Courses are offered in two semesters, fall and spring. Courses are offered at the undergraduate and graduate levels under the programs of its several departments of instruction: behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. Further inquiries regarding The Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, Md. 20014.

Seminars

An NIH Program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators, and gives them the additional opportunity to master selected topics not adequately covered during college or graduate schooling. These seminars are now administered by the Foundation for Advanced Education in the Sciences, Inc., in conjunction with the evening courses. The program accommodates Research, Staff, and Clinical Associates and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics; cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of an expert in the field. In preparation for these, the Associate does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate Institutes engaged in clinical research, the Clinical Center sponsors at least one monthly Combined Clinical Staff Conference for 8 months of the year. Each conference is conducted by one of the Institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff, and serve to keep individual investigators abreast of current emphasis in all clinical research.

Several formal lectures are presented annually. The National Institutes of Health Lecture Series was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the Scientific Directors of the Institutes. The R. E. Dyer Lectureship was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science; it is administered by NIH.

The Jules Freund lecture series was established in 1961 and is presented annually in honor of the first Chief of the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases.

The G. Burroughs Mider Lectureship was established in 1968 by the Scientific Directors to honor Dr. Mider for his distinguished service to NIH. On advice of the Scientific Directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Equipment Exhibit: Symposia

The NIH Research Equipment Exhibit was established in 1951 to acquaint scientists with the most modern research tools and to give them an opportunity to discuss equipment problems with representatives of industry. In 1954, a Symposium on Recent Developments in Research Methods and Instrumentation was added, offering a balanced presentation by specialists in many areas of biomedical research. The two annual events combined to provide a convenient setting for the exchange of information between research investigators and manufacturers of scientific equipment.

The NIH International Symposium on Biomedical Research was established in 1963 to emphasize the mutuality of interest of NIH and the international scientific community, particularly with the extension of NIH programs overseas.

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of

Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Naval Medical Center, offer exceptional opportunities. Some Associates find the time to pursue a certain amount of formal education at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located in the Clinical Center) provides a central facility for the scientific, medical, administrative and supportive staff engaged in the NIH research program. As a self-service, open-stack library, it contains a collection of 110,000 volumes and receives annually 5,000 monographs and 3,000 foreign and domestic journals. In addition to the usual library services, the NIH Library provides on-line access to NLM's medical literature data banks, advisory services for literature needs, and a translating service.

The National Library of Medicine is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 1 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service.

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